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[Diagnostic Test Accuracy Review]

Xpert MTB/RIF Ultra and Xpert MTB/RIF assays for extrapulmonary tuberculosis and rifampicin resistance in adults

Mikashmi Kohli[1], Ian Schiller[2], Nandini Dendukuri[2], Mandy Yao[2], Keertan Dheda[3,4], Claudia M Denkinger[5,6], Samuel G Schumacher[5], Karen R Steingart[7]

[1]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada. [2]Centre for Outcomes Research, McGill University Health Centre - Research Institute, Montreal, Canada. [3]Centre for Lung Infection and Immunity Unit, Department of Medicine and UCT Lung Institute, University of Cape Town, Cape Town, South Africa. [4]Faculty of Infectious and Tropical Diseases, Department of Immunology and Infection, London School of Hygiene and Tropical Medicine, London, UK. [5]FIND, Geneva , Switzerland. [6]Division of Tropical Medicine, Centre for Infectious Diseases, University Hospital Heidelberg, Heidelberg, Germany. [7]Honorary Research Fellow, Department of Clinical Sciences, Liverpool School of Tropical Medicine, Liverpool, UK

Contact address: Karen R Steingart, karen.steingart@gmail.com.

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ABSTRACT

Background

Xpert MTB/RIF Ultra (Xpert Ultra) and Xpert MTB/RIF are World Health Organization (WHO)-recommended rapid nucleic acid amplification tests (NAATs) widely used for simultaneous detection of *Mycobacterium tuberculosis* complex and rifampicin resistance in sputum. To extend our previous review on extrapulmonary tuberculosis (Kohli 2018), we performed this update to inform updated WHO policy (WHO Consolidated Guidelines (Module 3) 2020).

Objectives

To estimate diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for extrapulmonary tuberculosis and rifampicin resistance in adults with presumptive extrapulmonary tuberculosis.

Search methods

Cochrane Infectious Diseases Group Specialized Register, MEDLINE, Embase, Science Citation Index, Web of Science, Latin American Caribbean Health Sciences Literature, Scopus, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform, the International Standard Randomized Controlled Trial Number Registry, and ProQuest, 2 August 2019 and 28 January 2020 (Xpert Ultra studies), without language restriction.

Selection criteria

Cross-sectional and cohort studies using non-respiratory specimens. Forms of extrapulmonary tuberculosis: tuberculous meningitis and pleural, lymph node, bone or joint, genitourinary, peritoneal, pericardial, disseminated tuberculosis. Reference standards were culture and a study-defined composite reference standard (tuberculosis detection); phenotypic drug susceptibility testing and line probe assays (rifampicin resistance detection).

Data collection and analysis

Two review authors independently extracted data and assessed risk of bias and applicability using QUADAS-2. For tuberculosis detection, we performed separate analyses by specimen type and reference standard using the bivariate model to estimate pooled sensitivity and specificity with 95% credible intervals (CrIs). We applied a latent class meta-analysis model to three forms of extrapulmonary tuberculosis. We assessed certainty of evidence using GRADE.

Main results

69 studies: 67 evaluated Xpert MTB/RIF and 11 evaluated Xpert Ultra, of which nine evaluated both tests. Most studies were conducted in China, India, South Africa, and Uganda. Overall, risk of bias was low for patient selection, index test, and flow and timing domains, and low (49%) or unclear (43%) for the reference standard domain. Applicability for the patient selection domain was unclear for most studies because we were unsure of the clinical settings.

Cerebrospinal fluid

Xpert Ultra (6 studies)

Xpert Ultra pooled sensitivity and specificity (95% CrI) against culture were 89.4% (79.1 to 95.6) (89 participants; low-certainty evidence) and 91.2% (83.2 to 95.7) (386 participants; moderate-certainty evidence). Of 1000 people where 100 have tuberculous meningitis, 168 would be Xpert Ultra-positive: of these, 79 (47%) would not have tuberculosis (false-positives) and 832 would be Xpert Ultra-negative: of these, 11 (1%) would have tuberculosis (false-negatives).

Xpert MTB/RIF (30 studies)

Xpert MTB/RIF pooled sensitivity and specificity against culture were 71.1% (62.8 to 79.1) (571 participants; moderate-certainty evidence) and 96.9% (95.4 to 98.0) (2824 participants; high-certainty evidence). Of 1000 people where 100 have tuberculous meningitis, 99 would be Xpert MTB/RIF-positive: of these, 28 (28%) would not have tuberculosis; and 901 would be Xpert MTB/RIF-negative: of these, 29 (3%) would have tuberculosis.

Pleural fluid

Xpert Ultra (4 studies)

Xpert Ultra pooled sensitivity and specificity against culture were 75.0% (58.0 to 86.4) (158 participants; very low-certainty evidence) and 87.0% (63.1 to 97.9) (240 participants; very low-certainty evidence). Of 1000 people where 100 have pleural tuberculosis, 192 would be Xpert Ultra-positive: of these, 117 (61%) would not have tuberculosis; and 808 would be Xpert Ultra-negative: of these, 25 (3%) would have tuberculosis.

Xpert MTB/RIF (25 studies)

Xpert MTB/RIF pooled sensitivity and specificity against culture were 49.5% (39.8 to 59.9) (644 participants; low-certainty evidence) and 98.9% (97.6 to 99.7) (2421 participants; high-certainty evidence). Of 1000 people where 100 have pleural tuberculosis, 60 would be Xpert MTB/RIF-positive: of these, 10 (17%) would not have tuberculosis; and 940 would be Xpert MTB/RIF-negative: of these, 50 (5%) would have tuberculosis.

Lymph node aspirate

Xpert Ultra (1 study)

Xpert Ultra sensitivity and specificity (95% confidence interval) against composite reference standard were 70% (51 to 85) (30 participants; very low-certainty evidence) and 100% (92 to 100) (43 participants; low-certainty evidence). Of 1000 people where 100 have lymph node tuberculosis, 70 would be Xpert Ultra-positive and 0 (0%) would not have tuberculosis; 930 would be Xpert Ultra-negative and 30 (3%) would have tuberculosis.

Xpert MTB/RIF (4 studies)

Xpert MTB/RIF pooled sensitivity and specificity against composite reference standard were 81.6% (61.9 to 93.3) (377 participants; low-certainty evidence) and 96.4% (91.3 to 98.6) (302 participants; low-certainty evidence). Of 1000 people where 100 have lymph node tuberculosis, 118 would be Xpert MTB/RIF-positive and 37 (31%) would not have tuberculosis; 882 would be Xpert MTB/RIF-negative and 19 (2%) would have tuberculosis.

In lymph node aspirate, Xpert MTB/RIF pooled specificity against culture was 86.2% (78.0 to 92.3), lower than that against a composite reference standard. Using the latent class model, Xpert MTB/RIF pooled specificity was 99.5% (99.1 to 99.7), similar to that observed with a composite reference standard.

Rifampicin resistance

Xpert Ultra (4 studies)

Xpert Ultra pooled sensitivity and specificity were 100.0% (95.1 to 100.0), (24 participants; low-certainty evidence) and 100.0% (99.0 to 100.0) (105 participants; moderate-certainty evidence). Of 1000 people where 100 have rifampicin resistance, 100 would be Xpert Ultra-positive (resistant): of these, zero (0%) would not have rifampicin resistance; and 900 would be Xpert Ultra-negative (susceptible): of these, zero (0%) would have rifampicin resistance.

Xpert MTB/RIF (19 studies)

Xpert MTB/RIF pooled sensitivity and specificity were 96.5% (91.9 to 98.8) (148 participants; high-certainty evidence) and 99.1% (98.0 to 99.7) (822 participants; high-certainty evidence). Of 1000 people where 100 have rifampicin resistance, 105 would be Xpert MTB/RIF-positive (resistant): of these, 8 (8%) would not have rifampicin resistance; and 895 would be Xpert MTB/RIF-negative (susceptible): of these, 3 (0.3%) would have rifampicin resistance.

Authors' conclusions

Xpert Ultra and Xpert MTB/RIF may be helpful in diagnosing extrapulmonary tuberculosis. Sensitivity varies across different extrapulmonary specimens: while for most specimens specificity is high, the tests rarely yield a positive result for people without tuberculosis. For tuberculous meningitis, Xpert Ultra had higher sensitivity and lower specificity than Xpert MTB/RIF against culture. Xpert Ultra and Xpert MTB/RIF had similar sensitivity and specificity for rifampicin resistance. Future research should acknowledge the concern associated with culture as a reference standard in paucibacillary specimens and consider ways to address this limitation.

PLAIN LANGUAGE SUMMARY

How accurate are tests (Xpert Ultra and Xpert MTB/RIF) for diagnosing tuberculosis outside the lungs (extrapulmonary tuberculosis) and rifampicin resistance?

Why is using Xpert tests for extrapulmonary tuberculosis important?

Tuberculosis is one of the top 10 causes of death worldwide. Tuberculosis mainly affects the lungs (pulmonary) but may occur in other parts of the body (extrapulmonary). When people receive proper and timely treatment, tuberculosis is usually curable. One problem involved in managing tuberculosis is that the bacteria become resistant to antibiotics. Not recognizing tuberculosis early may result in delayed diagnosis and treatment and increased illness and death. An incorrect tuberculosis diagnosis may result in increased anxiety and unnecessary treatment.

What is the aim of this review?

To update the evidence on accuracy of Xpert tests for diagnosing extrapulmonary tuberculosis and rifampicin resistance in adults. Rifampicin is an important tuberculosis drug. We included tuberculous meningitis and pleural, lymph node, bone or joint, genitourinary, peritoneal, pericardial, and disseminated tuberculosis.

What was studied in this review?

Xpert Ultra and Xpert MTB/RIF are rapid tests for simultaneously diagnosing tuberculosis and rifampicin resistance. We combined study results to determine:
- sensitivity: people with tuberculosis (rifampicin resistance) correctly diagnosed as having the condition.
- specificity: people without tuberculosis (rifampicin resistance) correctly identified as not having the condition.
The closer sensitivity and specificity are to 100%, the better the test. We measured Xpert results against culture and a composite reference standard (neither is a perfect reference standard because extrapulmonary tuberculosis is paucibacillary (few bacteria)).

What are the main results in this review?

69 studies tested lymph node, pleural, and cerebrospinal fluid, and other specimens from people with presumptive extrapulmonary tuberculosis. Studies were conducted in 28 different countries.

For every 1000 people tested, if 100 had tuberculosis according to the reference standards:

cerebrospinal fluid

-*Xpert Ultra (6 studies)*:

· 89% sensitivity: 168 people would test positive, including 79 without tuberculosis

· 91% specificity: 832 people would test negative, including 11 with tuberculosis

- *Xpert MTB/RIF (30 studies)*:

· 71% sensitivity: 99 people would test positive, including 28 without tuberculosis

· 97% specificity: 901 people would test negative, including 29 with tuberculosis

pleural fluid

- *Xpert Ultra (4 studies)*:

· 75% sensitivity: 192 people would test positive, including 117 without tuberculosis

· 87% specificity: 808 people would test negative, including 25 with tuberculosis

- *Xpert MTB/RIF (25 studies)*:

· 50% sensitivity: 60 people would test positive, including 10 without tuberculosis

· 99% specificity: 940 would test negative, including 50 with tuberculosis

lymph node fluid

- *Xpert Ultra (1 study)*:

· 70% sensitivity: 70 people would test positive (all have tuberculosis)

· 100% specificity: 930 people would test negative, including 30 with tuberculosis

-*Xpert MTB/RIF (4 studies):*

· 82% sensitivity:118 people would test positive, including 37 without tuberculosis

· 96% specificity: 882 people would test negative, including 19 with tuberculosis

rifampicin resistance

-*Xpert Ultra (4 studies)*:

· 100% sensitivity: 100 people would test positive (all have rifampicin resistance)

· 100% specificity: 900 people would test negative (none have rifampicin resistance)

- *MTB/RIF test (19 studies)*:

· 97% sensitivity: 105 people would test positive, including eight without rifampicin resistance

· 99% specificity: 895 people would test negative, including three with rifampicin resistance

Who do the results of this review apply to?

People thought to have extrapulmonary tuberculosis.

How confident are we in our results?

Fairly confident for Xpert MTB/RIF in cerebrospinal fluid and less so in lymph node fluid. Less confident for Xpert Ultra, as there were few studies and few people tested. Both reference standards are imperfect, which may affect accuracy estimates.

What are the implications of this review?

The Xpert tests may be helpful in diagnosing extrapulmonary tuberculosis. Sensitivity varies across different extrapulmonary specimens, while for most specimens, specificity is high, the test rarely yielding a positive result for people without tuberculosis (verified by culture). For tuberculous meningitis, Xpert Ultra had higher sensitivity than Xpert MTB/RIF and lower specificity than Xpert MTB/RIF. The tests had similar accuracy for diagnosing rifampicin resistance.

How up-to-date is this review?

28 January 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Xpert Ultra and Xpert MTB/RIF in cerebrospinal fluid

Participants: people presumed to have tuberculous meningitis

Prior testing: people who received Xpert Ultra or Xpert MTB/RIF testing may first have undergone a health examination (history and physical examination) and possibly received a chest radiograph

Role: initial test, replacement for usual practice

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index tests: Xpert Ultra and Xpert MTB/RIF

Reference standard: solid or liquid culture

Studies: cross-sectional studies

Limitations: participants were evaluated exclusively as inpatients at a tertiary care centre, or, if the clinical setting was not reported, Xpert was performed at a reference laboratory rather than at primary care facilities and local hospitals

Xpert Ultra pooled sensitivity (95% CrI): 89.4% (79.1 to 95.6); pooled specificity (95% CrI): 91.2% (83.2 to 95.7)

Xpert MTB/RIF pooled sensitivity (95% CrI): 71.1% (62.8 to 79.1); pooled specificity (95% CrI): 96.9% (95.4 to 98.0)

Xpert Ultra result	1000 people tested for TB using Xpert Ultra (95% CrI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence of 2.5%	Prevalence of 10%	Prevalence of 20%		
True-positives (participants with TB meningitis)	22 (20 to 24)	89 (79 to 96)	178 (158 to 191)	89 (6)	⊕⊕⊖⊖ Low[a]
False-negatives (participants incorrectly classified as not having TB meningitis)	3 (1 to 5)	11 (4 to 21)	22 (9 to 42)		
True-negatives (participants without TB meningitis)	889 (811 to 933)	821 (749 to 861)	730 (666 to 766)	386 (6)	⊕⊕⊕⊖ Moderate[b]
False-positives (participants incorrectly classified as having TB meningitis)	86 (42 to 164)	79 (39 to 151)	70 (34 to 134)		

Xpert MTB/RIF result	1000 people tested for TB using XpertMTB/RIF (95% CrI)			Number of participants (studies)	Certainty of the evidence (GRADE)
	Prevalence of 2.5%	Prevalence of 10%	Prevalence of 20%		
True-positives (participants with TB meningitis)	18 (16 to 20)	71 (63 to 79)	142 (126 to 158)	571 (30)	⊕⊕⊕⊖ Moderate[c]
False-negatives (participants incorrectly classified as not having TB meningitis)	7 (5 to 9)	29 (21 to 37)	58 (42 to 74)		
True-negatives (participants without TB meningitis)	945 (930 to 956)	872 (859 to 882)	775 (763 to 784)	2824 (30)	⊕⊕⊕⊕ High
False-positives (participants incorrectly classified as having TB meningitis)	30 (19 to 45)	28 (18 to 41)	25 (16 to 37)		

Abbreviations: CrI: credible interval; TB: tuberculosis
We included plausible prevalence estimates for the target condition suggested by the WHO. For Xpert Ultra, the median prevalence of tuberculosis in the included studies was 35.2%. For Xpert MTB/RIF, the median prevalence of tuberculosis in the included studies was 15.2%.
Credible limits were estimated based on those around the point estimates for pooled sensitivity and specificity.
[a]There were few participants in this analysis. The very wide 95% CrI around true-positives and false-negatives may lead to different decisions, depending on which credible limits are assumed. We downgraded two levels for imprecision.
[b]The wide 95% CrI around true-negatives and false-positives would likely lead to different decisions, depending on which credible limits are assumed. We downgraded one level for imprecision.
[c]The wide 95% CrI around true-positives and false-negatives may lead to different decisions, depending on which credible limits are assumed. We downgraded one level for imprecision.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Summary of findings 2. Xpert Ultra and Xpert MTB/RIF in pleural fluid

Participants: people presumed to have pleural tuberculosis

Prior testing: people who received Xpert Ultra or Xpert MTB/RIF testing may first have undergone a health examination (history and physical examination) and received a chest radiograph

Role: initial test, replacement for usual practice, which may include more invasive tests, such as pleural biopsy

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index tests: Xpert Ultra and Xpert MTB/RIF

Reference standard: solid or liquid culture

Studies: cross-sectional studies

Limitations: in most studies, participants were evaluated at a tertiary care centre, or if the clinical setting was not reported, the test was performed at a reference laboratory

Xpert Ultra pooled sensitivity (95% CrI): 75.0% (58.0 to 86.4); pooled specificity (95% CrI): 87.0% (63.1 to 97.9)

Xpert MTB/RIF pooled sensitivity (95% CrI): 49.5% (39.8 to 59.9); pooled specificity (95% CrI): 98.9% (97.6 to 99.7)

Xpert Ultra result	**1000 people tested for TB using Xpert Ultra (95% CrI)**			**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
	Prevalence of 2.5%	**Prevalence of 10%**	**Prevalence of 20%**		
True-positives (patients with pleural TB)	19 (14 to 22)	75 (58 to 86)	150 (116 to 173)	158 (4)	⊕⊝⊝⊝ Very low[a,b,c]
False-negatives (patients incorrectly classified as not having pleural TB)	6 (3 to 11)	25 (14 to 42)	50 (27 to 84)		
True-negatives (patients without pleural TB)	848 (615 to 955)	783 (568 to 881)	696 (505 to 783)	240 (4)	⊕⊝⊝⊝ Very low[a,d,e]
False-positives (patients incorrectly classified as having pleural TB)	127 (20 to 360)	117 (19 to 332)	104 (17 to 295)		
Xpert MTB/RIF result	**1000 people tested for TB using Xpert MTB/RIF (95% CrI)**			**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
	Prevalence of 2.5%	**Prevalence of 10%**	**Prevalence of 20%**		
True-positives (patients with pleural TB)	12	50	99	644 (25)	⊕⊕⊝⊝ Low[f,g,h]

	(10 to 15)	(40 to 60)	(80 to 120)		
False-negatives (patients incorrectly classified as not having pleural TB)	13 (10 to 15)	50 (40 to 60)	101 (80 to 120)		
True-negatives (patients without pleural TB)	964 (952 to 972)	890 (878 to 897)	791 (781 to 798)	2421 (25)	⊕⊕⊕⊕ High
False-positives (patients incorrectly classified as having pleural TB)	11 (3 to 23)	10 (3 to 22)	9 (2 to 19)		

Abbreviations: CrI: credible interval; TB: tuberculosis.
We included plausible prevalence estimates for the target condition suggested by the WHO. For Xpert Ultra, the median prevalence of tuberculosis in the included studies was 46.2%. For Xpert MTB/RIF, the median prevalence of tuberculosis in the included studies was 19.8%.
[a]We were interested in how Xpert Ultra performed in patients presumed to have extrapulmonary tuberculosis who were evaluated as they would be in routine practice. However, most studies did not report information on the clinical setting. We downgraded one level for indirectness.
[b]For individual studies, sensitivity estimates ranged from 48% to 84%. We could not explain the heterogeneity by study quality or other factors. We downgraded one level for inconsistency.
[c]There was a low number of participants contributing to this analysis for the observed sensitivity. As we had already downgraded for inconsistency, we downgraded one level for imprecision.
[d]For individual studies, specificity estimates ranged from 65% to 100%. We could not explain the heterogeneity by study quality or other factors. We downgraded one level for inconsistency.
[e]We thought the wide 95% CrI around false-positives and true-negatives would likely lead to different decisions depending on which confidence limits are assumed. As we had already downgraded for inconsistency, we downgraded one level for imprecision.
[f]We were interested in how Xpert MTB/RIF performed in participants presumed to have extrapulmonary tuberculosis who were evaluated as they would be in routine practice. However, most studies did not report information on the clinical setting. We downgraded one level for indirectness.
[g]For individual studies, sensitivity estimates ranged from 10% to 100%. We could not explain the heterogeneity by study quality or other factors. We downgraded one level for inconsistency.
[h]As we had already downgraded for inconsistency, we did not downgrade further for imprecision.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Summary of findings 3. Xpert Ultra and Xpert MTB/RIF in lymph node aspirate

Participants: people presumed to have lymph node tuberculosis

Prior testing: people who received Xpert testing may first have undergone a health examination (history and physical examination) and possibly received a chest radiograph

Role: initial test, replacement for usual practice, which may include more invasive tests, such as biopsy of affected organs

Settings: primarily tertiary care centres (the index test was often run in reference laboratories)

Index tests: Xpert Ultra and Xpert MTB/RIF

Reference standard: composite reference standard

Studies: cross-sectional studies

Limitations: in most studies, participants were evaluated at a tertiary care centre, or if the clinical setting was not reported, the test was performed at a reference laboratory performed at a reference laboratory

Xpert Ultra sensitivity (95% CI): 70% (51 to 85); specificity: 100% (92 to 100)

Xpert MTB/RIF pooled sensitivity (95% CrI): 81.6% (61.9 to 93.3); pooled specificity: 96.4% (91.3 to 98.6)

Xpert Ultra result	**1000 people tested for TB using Xpert Ultra (95% CI)**			**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
	Prevalence of 2.5%	**Prevalence of 10%**	**Prevalence of 20%**		
True-positives (patients with lymph node TB)	17 (13 to 21)	70 (51 to 85)	140 (102 to 170)	30 (1)	⊕⊝⊝⊝ Very low[a,b]
False-negatives (patients incorrectly classified as not having lymph node TB)	8 (4 to 12)	30 (15 to 49)	60 (30 to 98)		
True-negatives (patients without lymph node TB)	975 (897 to 975)	900 (828 to 900)	800 (736 to 800)	43 (1)	⊕⊝⊝⊝ Very low[a,c]
False-positives (patients incorrectly classified as having lymph node TB)	0 (0 to 78)	0 (0 to 72)	0 (0 to 64)		
Xpert MTB/RIF result	**1000 people tested for TB using Xpert MTB/RIF (95% CrI)**			**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
	Prevalence of 2.5%	**Prevalence of 10%**	**Prevalence of 20%**		
True-positives (patients with lymph node TB)	20 (16 to 23)	81 (62 to 92)	162 (124 to 184)	377 (4)	⊕⊕⊝⊝ Low[d,e]
False-negatives (patients incorrectly classified as not having lymph node TB)	5 (2 to 9)	19 (8 to 38)	38 (16 to 76)		
True-negatives (patients without lymph node TB)	935 (878 to 958)	863 (811 to 885)	767 (721 to 786)	302 (4)	⊕⊕⊝⊝ Low[d,e]

False-positives (patients incorrectly classified as having lymph node TB)	40 (17 to 97)	37 (15 to 89)	33 (14 to 79)

Abbreviations: CrI: credible interval; TB: tuberculosis.
We included plausible prevalence estimates for the target condition suggested by the WHO. For Xpert Ultra, the prevalence of tuberculosis in the included study was 41%. For Xpert MTB/RIF, the median prevalence of tuberculosis in the included studies was 55.5%.
[a]We identified only one study, which was conducted at a tertiary referral centre in South Africa, a high TB burden country. Most participants (84%) were seen as outpatients. With only one study, applicability to other settings comes with some uncertainty. We downgraded one level for indirectness.
[b]There were very few participants contributing to this analysis. The 95% CI was very wide. We downgraded two levels for imprecision.
[c]There were very few participants contributing to this analysis. The 95% CI was wide. We downgraded two levels for imprecision.
[d]The composite reference standard was defined by the primary study authors and therefore, was not uniform. We downgraded one level for risk of bias.
[e]For indirectness, regarding applicability, for the patient population, we considered most studies to have unclear concern. We were interested in how Xpert MTB/RIF performed in patients presumed to have extrapulmonary TB who were evaluated as they would be in routine practice. However, none of the studies reported this information. We downgraded one level for indirectness.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

Summary of findings 4. Xpert Ultra and Xpert MTB/RIF for rifampicin resistance

Participants: people with tuberculosis detected by Xpert Ultra or Xpert MTB/RIF

Role: initial test**,** replacement test for standard practice, which includes culture-based drug susceptibility testing or line probe assay

Settings: primarily tertiary care centres, the index test was often run in central (reference laboratories), where drug susceptibility testing for the reference standard could be performed

Index tests: Xpert Ultra and Xpert MTB/RIF

Reference standard: culture-based drug susceptibility testing using solid or liquid media or line probe assay

Studies: cross-sectional studies

Xpert Ultra pooled sensitivity (95% CrI): 100.0% (95.1 to 100.0); pooled specificity (95% CrI): 100.0% (99.0 to 100.0)

Xpert MTB/RIF pooled sensitivity (95% CrI): 96.5% (91.9 to 98.8); pooled specificity (95% CrI): 99.1% (98.0 to 99.7)

Xpert Ultra result	1000 people tested for rifampicin resistance using Xpert Ultra (95% CrI)	Number of participants (studies)	Certainty of the evidence (GRADE)

	Prevalence of 2%	Prevalence of 10%	Prevalence of 15%		
True-positives (patients correctly classified as rifampicin resistant)	20 (19 to 20)	100 (95 to 100)	150 (143 to 150)	24 (4)	⊕⊕⊖⊖ Low[a,b]
False-negatives (patients incorrectly classified as rifampicin susceptible)	0 (0 to 1)	0 (0 to 5)	0 (0 to 7)		
True-negatives (patients correctly classified as rifampicin susceptible)	980 (979 to 980)	900 (899 to 900)	850 (849 to 850)	105 (4)	⊕⊕⊕⊖ Moderate[a]
False-positives (patients incorrectly classified as rifampicin resistant)	0 (0 to 1)	0 (0 to 1)	0 (0 to 1)		
Xpert MTB/RIF result	**1000 people tested for rifampicin resistance using Xpert MTB/RIF (95% CrI)**			**Number of participants (studies)**	**Certainty of the evidence (GRADE)**
	Prevalence of 2%	**Prevalence of 10%**	**Prevalence of 15%**		
True-positives (patients correctly classified as rifampicin resistant)	19 (18 to 20)	97 (92 to 99)	145 (138 to 148)	148 (19)	⊕⊕⊕⊕ High
False-negatives (patients incorrectly classified as rifampicin susceptible)	1 (0 to 2)	3 (1 to 8)	5 (2 to 12)		
True-negatives (patients correctly classified as rifampicin susceptible)	971 (960 to 977)	892 (882 to 897)	842 (833 to 847)	822 (19)	⊕⊕⊕⊕ High
False-positives (patients incorrectly classified as rifampicin resistant)	9 (3 to 20)	8 (3 to 18)	8 (3 to 17)		

Abbreviations: CrI: credible interval; TB: tuberculosis.
We included plausible prevalence estimates for the target condition suggested by the WHO. For Xpert Ultra, the median prevalence of rifampicin resistance in the included studies was 19.2%. For Xpert MTB/RIF, the median prevalence of rifampicin resistance in the included studies was 11.9%.
[a]All these studies were conducted in China (high TB-burden country). Applicability to other settings comes with some uncertainty and therefore we downgraded one level for indirectness.
[b]There was a low number of participants contributing to this analysis for the observed sensitivity. We downgraded one level for imprecision.
GRADE certainty of the evidence
High: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.
The results presented in this table should not be interpreted in isolation from results of the individual included studies contributing to each summary test accuracy measure.

BACKGROUND

Tuberculosis (TB) causes tremendous suffering worldwide and has surpassed HIV/AIDS as the world's leading infectious cause of death. The World Health Organization (WHO) estimates that globally in 2019, 10.0 million (range, 8.9 to 11.0 million) people fell ill with tuberculosis. In 2019, around 1.2 million HIV-negative people died from tuberculosis and 208,000 HIV-positive people died from tuberculosis (WHO Global TB Report 2020). When people receive proper treatment, tuberculosis is treatable and curable. The WHO estimates that from 2000 to 2019 more than 60 million lives were saved by diagnosing and treating tuberculosis. However, the COVID-19 pandemic threatens the gains made over recent years. A modelling study by the WHO suggests that there could be between 200,000 and 400,000 additional tuberculosis deaths in 2020 if, over a period of three months, 25% to 50% fewer people were detected and treated with tuberculosis (WHO Global TB Report 2020).

Of the 7.1 million new cases of tuberculosis notified to the WHO in 2019, 16% were cases of extrapulmonary tuberculosis, (range, 8% in the WHO Western Pacific Region to 24% in the WHO Eastern Mediterranean Region) (WHO Global TB Report 2020). Among countries in the European Union, extrapulmonary tuberculosis was responsible for 19% of all notified cases (range, 6% to 44%) (Sandgren 2013). A large retrospective analysis from China found that of 19,279 hospitalised tuberculosis patients, around 33% had extrapulmonary tuberculosis (Pang 2019). The number of people affected by extrapulmonary tuberculosis is likely to be higher, given that, according to the WHO, extrapulmonary tuberculosis is notified as pulmonary tuberculosis when the two forms exist together, and diagnosing extrapulmonary tuberculosis is challenging, as described below. Additionally, extrapulmonary tuberculosis accounts for an increasing proportion of tuberculosis cases in some countries, in part because of host and genetic considerations, and the association of extrapulmonary tuberculosis and HIV (Golden 2005; Pai 2016; Perkins 2007; Webster 2014). Based on surveillance and epidemiological data, extrapulmonary tuberculosis affects a greater proportion of children than adults (Nelson 2004).

Drug-resistant tuberculosis is a serious threat to global health. For the purpose of surveillance and treatment, drug-resistant tuberculosis is classified as rifampicin-resistant tuberculosis, multidrug-resistant tuberculosis (MDR-TB), and extensively drug-resistant tuberculosis. MDR-TB is defined as resistance to at least isoniazid and rifampicin, the two most important first-line anti-tuberculosis drugs. Extensively drug-resistant tuberculosis is defined as MDR-TB plus resistance to at least one drug in the following two classes of medicines used in treatment of MDR-TB: fluoroquinolones and second-line injectable agents. In 2019, there were approximately half a million new cases of rifampicin-resistant tuberculosis (of which 78% had MDR-TB), with India (27%), China (14%) and the Russian Federation (9%) accounting for the largest burden (WHO Global TB Report 2020). In 2019, 12,350 cases of extensively drug-resistant tuberculosis were reported (WHO Global TB Report 2020).

In 2014, the World Health Assembly unanimously approved the WHO End TB Strategy, a 20-year strategy devised to end the global tuberculosis epidemic (WHO END TB 2014). Early diagnosis of tuberculosis, including universal drug susceptibility testing (DST) and systematic screening of contacts and high-risk groups, is a part of pillar one of the strategy.

Target condition being diagnosed

Extrapulmonary TB

Tuberculosis is caused by infection with *Mycobacterium tuberculosis* (*M tuberculosis*) bacteria. Tuberculosis predominantly affects the lungs (pulmonary tuberculosis). Extrapulmonary tuberculosis refers to tuberculosis in parts of the body other than the lungs. Extrapulmonary tuberculosis is known to affect virtually every part of the body, with lymph nodes and the pleura being the most common sites (Sharma 2004). Although active pulmonary tuberculosis is transmissible by droplets spread by coughing, extrapulmonary tuberculosis is thought to result from hematogenous spread (spread by way of the bloodstream) from an initial lung infection and is not infectious. Extrapulmonary tuberculosis can occur alone or together with pulmonary tuberculosis.

The various forms of extrapulmonary tuberculosis cause signs and symptoms related to the structures affected. Table 1 describes the forms of extrapulmonary tuberculosis included in this review, as well as the respective specimens that may be collected for diagnosis.

Diagnosis of extrapulmonary tuberculosis is challenging for several reasons. Many forms of extrapulmonary tuberculosis require invasive diagnostic sampling; gathering adequate specimens can pose risk of harm to the patient and can be costly. Most forms of extrapulmonary tuberculosis are paucibacillary (tuberculosis disease caused by a small number of bacteria), making diagnosis by various tests less sensitive. Culture, for example, has reduced sensitivity in paucibacillary disease. In addition, culture takes several weeks for results and requires a highly-equipped laboratory. Limitations are also associated with histology, which relies on highly-trained operators, and characteristic morphology is shared with other diseases. As a result of these difficulties, diagnosis of extrapulmonary tuberculosis is often made on the grounds of clinical suspicion alone, and many people receive the wrong diagnosis, leading to unnecessary tuberculosis treatment or poor outcomes from untreated extrapulmonary tuberculosis.

Tuberculosis treatment regimens must contain multiple drugs to which the organisms are sensitive to cure tuberculosis and avoid selection for drug resistance. WHO tuberculosis treatment guidelines recommend the same drug regimens for extrapulmonary and pulmonary disease, with notable mention of tuberculous meningitis and bone or joint tuberculosis, for which longer treatment regimens are recommended (WHO 2010; WHO 2017; WHO Compendium 2018). For patients with tuberculous meningitis or tuberculous pericarditis, the use of adjuvant corticosteroid therapy is recommended in addition to appropriate tuberculosis treatment regimens (WHO 2017; WHO Compendium 2018). Other tuberculosis treatment guidelines include Sharma 2017b (India), and those issued by the American Thoracic Society, the Centers for Disease Control and Prevention (CDC), and the Infectious Diseases Society of America (Nahid 2016). The drugs used to treat MDR-TB are less potent and more toxic than the drugs used to treat drug-susceptible tuberculosis, historically requiring two years or more of therapy. However, in December 2019, based on new evidence on the management of drug-resistant tuberculosis, the WHO issued recommendations that all patients with MDR-TB or rifampicin-resistant tuberculosis, including those who are also

resistant to fluoroquinolones, may benefit from effective all-oral treatment regimens, either shorter or longer (WHO Consolidated Guidelines (Module 4) 2020).

Rifampicin resistance

Rifampicin inhibits bacterial DNA-dependent RNA polymerase, encoded by the RNA polymerase gene (*rpoB*) (Hartmann 1967). Resistance to this drug has been associated mainly with mutations in a limited region of the *rpoB* gene (Telenti 1993). Rifampicin resistance may occur alone or in association with resistance to isoniazid and other drugs. In settings with a high burden of MDR-TB, the presence of rifampicin resistance alone may serve as a proxy for MDR-TB (WHO 2011). People with drug-resistant tuberculosis can transmit the infection to others.

Index test(s)

The index tests, Xpert MTB/RIF and Ultra Xpert MTB/RIF (Xpert Ultra, the newest version) (Cepheid Inc, Sunnyvale, USA), are nucleic acid amplification tests (NAATs) (i.e. molecular tests) used for diagnosing tuberculosis and rifampicin-resistant tuberculosis. Xpert MTB/RIF and Xpert Ultra cartridges are used with the GeneXpert system (Cepheid 2018; Cepheid 2019). Xpert MTB/RIF and Xpert Ultra are able to detect both *M tuberculosis* complex and rifampicin resistance within two hours after starting the test, with minimal hands-on technical time. Unlike conventional NAATs, with Xpert MTB/RIF and Xpert Ultra, sample processing and polymerase chain reaction (PCR) amplification and detection are integrated into a single, self-enclosed test unit, the GeneXpert cartridge. Following sample loading, all steps in the assay are completely automated and self-contained. In addition, the assays' sample reagent, used to liquefy sputum, has potent tuberculocidal (the ability to kill tuberculosis bacteria) properties and so largely eliminates biosafety concerns during the test procedure (Banada 2010). Except as described below for Ultra trace call results, a single Xpert MTB/RIF or Xpert Ultra run will provide both detection of tuberculosis and detection of rifampicin resistance. One cannot deselect testing for rifampicin resistance and only run the assay for tuberculosis detection.

The development of Xpert MTB/RIF was a major step toward improving detection of tuberculosis and rifampicin resistance globally (Boehme 2010; Small 2011). Since Xpert MTB/RIF was released, there have been four generations (G1, G2, G3, and G4) of the test involving different software and cartridge combinations. Although in comparison with smear microscopy Xpert MTB/RIF has increased sensitivity for pulmonary tuberculosis (Steingart 2014), the test has suboptimal sensitivity in people with smear-negative and HIV-associated tuberculosis. A Cochrane Review on the diagnostic accuracy of Xpert MTB/RIF for pulmonary tuberculosis found pooled sensitivity and specificity (95% credible Interval (CrI)) of 85% (82% to 88%) and 98% (97% to 98%), (70 studies, 37,237 unselected participants; high-certainty evidence) (Horne 2019). However, Xpert MTB/RIF sensitivity was decreased in people with smear-negative culture-positive disease, pooled sensitivity of 67% (62% to 72%), and people living with HIV, pooled sensitivity of 81% (75% to 86%) (Horne 2019). Xpert MTB/RIF versions have also had some limitations in detecting rifampicin resistance.

In order to overcome limitations with Xpert MTB/RIF, Cepheid developed Xpert Ultra, a re-engineered assay that uses a newly-developed cartridge but may be run on the same device after a software upgrade. To improve sensitivity for tuberculosis detection, Xpert Ultra incorporates two different multi-copy amplification targets and a larger DNA reaction chamber than Xpert MTB/RIF (WHO Xpert Ultra 2017). A laboratory study reported that the limit of detection (the lowest number of colony-forming units (CFUs) per sample that can be reproducibly distinguished from negative samples with 95% confidence) using Xpert Ultra improved to 15.6 CFU/mL of sputum compared to 112.6 CFU/mL for Xpert MTB/RIF (Chakravorty 2017). Xpert Ultra has added a new result category, 'trace call', that corresponds to the lowest bacillary load for *M tuberculosis* detection (WHO Xpert Ultra 2017). This new category is reported as 'MTB trace DETECTED'. Interpreting a trace call result requires a reassessment of clinical symptoms and history of prior tuberculosis. No rifampicin resistance results are available (indeterminate) for people with trace results. As with Xpert MTB/RIF (Miotto 2012), Xpert Ultra detects both live and dead bacteria.

To address limitations in rifampicin resistance detection, Xpert Ultra uses melting temperature-based analysis, in lieu of real-time PCR analysis with Xpert MTB/RIF. Melting temperature-based analysis allows Xpert Ultra to better distinguish resistance-conferring mutations from silent mutations with improved diagnostic accuracy for rifampicin resistance detection (Global Laboratory Initiative 2017).

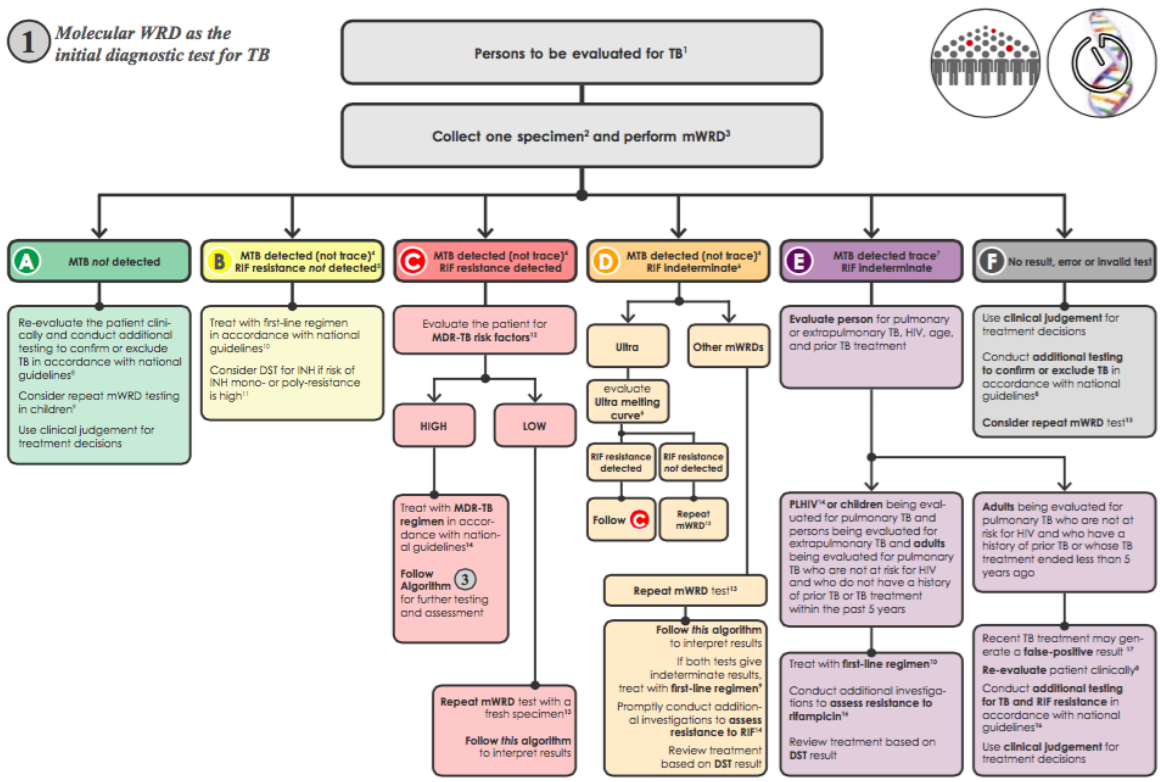
For sputum specimens, the test procedure may be used either directly on raw sputum specimens or sputum pellets created after decontaminating and concentrating the sputum (Blakemore 2010). In both cases, the test material is combined with the assay sample reagent (sodium hydroxide and isopropanol), mixed by hand or vortex, and incubated at room temperature for 15 minutes. After the incubation step, 2 mL of the treated specimen are transferred to the cartridge and the run is initiated (Helb 2010). According to the manufacturer, as with Xpert MTB/RIF, Xpert Ultra may be used with fresh sputum specimens, which may be either unprocessed sputum or processed sputum sediments. The sample reagent:sample volume ratio is 2:1 for unprocessed sputum and 3:1 for sputum pellets. The manufacturer does not specifically mention the use of the index tests with frozen specimens (Cepheid 2018; Cepheid 2019). As with Xpert MTB/RIF, Xpert Ultra using the GeneXpert sytem requires an uninterrupted and stable electrical power supply, temperature control, and yearly calibration of the cartridge modules (Global Laboratory Initiative 2019). Like previous Xpert cartridge generations, Xpert Ultra can be performed by operators with minimal technical expertise (Theron 2014a). The time to run the assay is shorter for Xpert Ultra (around 65 to 87 minutes) than for Xpert MTB/RIF (112 minutes) (Global Laboratory Initiative 2017). Currently, the manufacturer, Cepheid Incorporated (Sunnyvale, CA, USA), has made no claim for the use of Xpert Ultra and Xpert MTB/RIF in non-sputum specimens (Cepheid 2019). However, there is a standard operating procedure provided by WHO for processing non-sputum specimens (WHO 2014).

Clinical pathway

Xpert Ultra and Xpert MTB/RIF are used for the diagnosis of extrapulmonary tuberculosis and rifampicin resistance. Figure 1 shows the clinical pathway and presents the context in which Xpert Ultra or Xpert MTB/RIF might be used (WHO Operational Handbook Diagnosis (Module 3) 2020). The target conditions were extrapulmonary tuberculosis, which includes several forms

(e.g. tuberculous meningitis, pleural tuberculosis) and rifampicin resistance.

Figure 1. The clinical pathway describes how patients might present and the point in the pathway at which they would be considered for testing with Xpert Ultra or Xpert MTB/RIF. This algorithm for the use of a molecular WHO-recommended rapid diagnostic (WRD), which includes Xpert Ultra and Xpert MTB/ RIF, comes from the WHO operational handbook on tuberculosis (WHO Operational Handbook Diagnosis (Module 3) 2020). Copyright © [2020] [World Health Organization]: reproduced with permission. Abbreviations: DST: drug susceptibility testing; INH: isoniazid; MDR-TB: multidrug-resistant TB; MTB: Mycobacterium tuberculosis; PLHIV: people living with HIV; RIF: rifampicin; TB: tuberculosis; WRD: WHO-recommended rapid diagnostic, which includes Xpert Ultra and Xpert MTB/ RIF.



Before a specimen is tested, patients with presumptive extrapulmonary tuberculosis would have undergone a health examination (history and physical examination) and possibly a chest radiograph. The presentation of extrapulmonary tuberculosis varies depending on the body site affected, and it may imitate other diseases, such as cancer and bacterial and fungal infections. Signs and symptoms of extrapulmonary tuberculosis are often non-specific and may include fever, night sweats, fatigue, loss of appetite, and weight loss (as seen in pulmonary tuberculosis) or specific complaints related to the involved site (e.g. headache for tuberculous meningitis, back pain for tuberculosis of the spine). The clinical presentation of extrapulmonary disease may be acute but is more often subacute (falling between acute and chronic) or chronic, meaning that patients may have symptoms for days to months before they seek care.

We have described in Table 1 signs and symptoms of the forms of extrapulmonary tuberculosis included in this review. The clinician should take a careful history, noting history of tuberculosis exposure, prior tuberculosis disease, and medical conditions that increase the risk for tuberculosis disease (e.g. HIV, diabetes mellitus, low body weight). In comparison with HIV-negative people, HIV-positive people have higher rates of extrapulmonary tuberculosis or mycobacteraemia (tuberculosis bloodstream infection). HIV-positive patients with signs or symptoms of extrapulmonary tuberculosis should have specimens taken from the suspected site(s) of involvement to increase the likelihood of tuberculosis diagnosis. Tuberculous meningitis is the most severe form of tuberculosis. In tuberculous meningitis, diagnosis is often delayed, with appalling consequences for patients. For all forms of extrapulmonary tuberculosis, patients may be evaluated in primary- or secondary-care settings. However,

if more complex or invasive tests are needed, patients may be referred to a tertiary medical centre (Iseman 2000; Reuter 2009; Sharma 2004).

The downstream consequences of testing include the following.

- True-positive (TP): patients would benefit from rapid diagnosis and appropriate treatment.
- True-negative (TN): patients would be spared unnecessary treatment and would benefit from reassurance and pursuit of an alternative diagnosis.
- False-positive (FP): patients would likely experience anxiety and morbidity caused by additional testing, unnecessary treatment, and possible adverse effects; possible stigma associated with a tuberculosis or MDR-TB diagnosis; and the chance that a false-positive may halt further diagnostic evaluation.
- False-negative (FN): increased risk of morbidity and mortality and delayed treatment initiation for patients.

Role of index test(s)

We were interested in the following roles for testing.

I. Xpert Ultra and Xpert MTB/RIF for detection of extrapulmonary tuberculosis

Index test used as an initial test replacing usual practice (including conventional microscopy, culture or histopathology) for the diagnosis of extrapulmonary tuberculosis in adults with presumptive extrapulmonary tuberculosis (WHO Consolidated Guidelines (Module 3) 2020). An initial test does not mean that other tests will follow.

II. Xpert Ultra and Xpert MTB/RIF for detection of rifampicin resistance

Index test used as an initial test replacing culture and phenotypic DST for the diagnosis of rifampicin-resistant tuberculosis in adults with presumptive extrapulmonary tuberculosis (WHO Consolidated Guidelines (Module 3) 2020).

As mentioned, in high MDR-TB settings the presence of rifampicin resistance alone may serve as a proxy for MDR-TB. Xpert Ultra and Xpert MTB/RIF do not eliminate the need for subsequent culture and phenotypic DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

Alternative test(s)

For a comprehensive review of new tests not yet in widespread use, we refer the reader to Branigan 2019; Lewinsohn 2017; Unitaid 2017.

Smear microscopy (light microscopy (Ziehl-Neelsen), fluorescence microscopy, or light-emitting diode (LED) fluorescence microscopy) is the examination of smears for acid-fast bacilli (tuberculosis bacteria) under a microscope. Around 5000 to 10,000 organisms per mL must be present in the specimen for tuberculosis bacteria to be visible by microscopy (American Thoracic Society 2000). For extrapulmonary tuberculosis, microscopy can be performed in fluid or tissue specimens from sites of disease involvement, for example, in cerebrospinal fluid (CSF) in presumptive tuberculous meningitis or in lymph node tissue in presumptive lymph node tuberculosis. For most extrapulmonary sites, because there are usually few organisms, the sensitivity of smear microscopy is generally low. Ranges from studies, some with selected cases, are quoted here: 0% to 10% in pleural fluid; 14% to 39% in pleural tissue; 2% to 30% in CSF; < 5% in peritoneal fluid; and 0% to 42% in pericardial fluid. In contrast, the specificity of smear microscopy tends to be quite high, as can be seen in pulmonary tuberculosis (≥ 90%) (Kilpatrick 1986; Lewinsohn 2017).

Mycobacterial culture is a method used to grow bacteria on nutrient-rich media. In comparison with microscopy, a positive culture requires only around 100 organisms per mL and therefore can detect lower numbers of tuberculosis bacteria (American Thoracic Society 2000). Additionally, culture is essential for species identification and DST. However, culture takes several weeks and requires a highly-equipped laboratory. Culture has reduced sensitivity in paucibacillary disease (reference standards have included culture from a different specimen, such as sputum, smear microscopy, NAATs, presence of granulomatous inflammation, clinical criteria, imaging studies, and response to anti-tuberculosis therapy, done alone or in various combinations): CSF 45% to 70%; pleural fluid 23% to 58%; urine 80% to 90%; peritoneal tuberculosis 45% to 69%; pericardial tuberculosis 50% to 65% (Lewinsohn 2017); lymph node tuberculosis (excisional biopsy) 18% to 93%; and lymph node tuberculosis (fine-needle aspirate) 10% to 67% (Fontanilla 2011).

Histological examination involves examination of tissue specimens under a microscope. Diagnosis of extrapulmonary tuberculosis by histological examination is based on finding acid-fast bacilli and granulomatous inflammation, frequently with caseous (cheese-like) necrosis (necrotizing granulomas). The sensitivity of histology has been reported to vary for different forms of extrapulmonary tuberculosis (reference standards have included smear microscopy, culture, NAATs, clinical criteria, and imaging studies, done alone or in various combinations): 59% to 88% for lymph node tuberculosis (excisional biopsy) (Fontanilla 2011); 69% to 97% in pleural tissue (closed pleural biopsy); 86% to 94% in urological tissue; 60% to 70% in endometrial curettage; 79% to 100% in peritoneal biopsy; and 73% to 100% in pericardial tissue (Lewinsohn 2017). Sensitivity has also been observed to vary for different diagnostic techniques. Diacon 2003 found thoracoscopy to be more sensitive (sensitivity of 100%) than closed-needle biopsy (sensitivity of 66%) for establishing a diagnosis of pleural tuberculosis (reference standards have included microscopy smear, culture, or presence of granulomatous inflammation with caseous necrosis). Specificity has been observed to be low because of the presence of granulomas in other diseases, both infectious and non-infectious (Lewinsohn 2017), although the presence of 'necrotizing' granulomatous inflammation increases specificity (Woodard 1982). Histological examination carries the additional concern that invasive procedures that are complex and costly may be required to obtain the necessary specimens (Golden 2005).

Cytopathological examination of fluid specimens (such as pleural and peritoneal fluid) may be performed, first to exclude cancer, and then to obtain material for additional analyses, such as measurement of levels of adenosine deaminase and free interferon-gamma (IFN-γ) and cell counts (Lewinsohn 2017; Wright 2009a). Advantages of these tests include that they are rapid and simple and can be performed in most clinical laboratories (Dinnes 2007). In pleural, pericardial, and peritoneal fluid, a predominance of lymphocytes, especially in the absence of mesothelial cells, is highly suggestive of tuberculosis (Wright 2009a). However, in HIV-

positive people, this pattern may not be observed (Wright 2009a). Adenosine deaminase, an enzyme involved in purine metabolism, has been extensively studied for its potential role in the diagnosis of pleural tuberculosis, peritoneal tuberculosis, and tuberculous meningitis (Lewinsohn 2017). IFN-γ is released after it is sensitized by T cells in response to specific *M tuberculosis* antigens. A recent review of the evidence using GRADE provides the following recommendations.

- "...cell counts and chemistries be performed on amenable fluid specimens (including include pleural, cerebrospinal, ascitic, and joint fluid) collected from sites of suspected extrapulmonary TB (conditional recommendation, very low-quality evidence).
- ...adenosine deaminase levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB, TB meningitis, peritoneal TB, or pericardial TB (conditional recommendation, low-quality evidence).
- ...free IFN-γ levels be measured, rather than not measured, on fluid collected from patients with suspected pleural TB or peritoneal TB (conditional recommendation, low-quality evidence)" (Lewinsohn 2017).

NAAT is a molecular technique that can detect small quantities of genetic material (DNA or RNA) from micro-organisms, such as *M tuberculosis.* The key advantage of NAATs is that they are rapid diagnostic tests, potentially providing results in a few hours. This is a particularly important feature of the test in life-threatening forms of extrapulmonary tuberculosis, such as tuberculous meningitis. A variety of molecular amplification methods are available, of which PCR is the most common. NAATs are available as commercial kits and in-house tests (based on a protocol developed in a laboratory) and are used routinely in high-income countries for tuberculosis detection. In-house PCR is widely used in low-income countries because these tests are less expensive than commercial kits. An older editorial summarizing three systematic reviews (140 studies) of commercial and in-house NAATs (other than Xpert MTB/RIF) for different forms of extrapulmonary tuberculosis found relatively low sensitivity and underscored concerns about the cost and feasibility of this technology in resource-limited areas (Pai 2008). Similarly, another systematic review found that NAATs have relatively low sensitivity for extrapulmonary tuberculosis but high specificity (e.g. for tuberculous meningitis, for pleural TB), indicating that these tests cannot be used reliably to rule out tuberculosis (Dinnes 2007). A recent evidence synthesis reported sensitivities of 72% to 88% in lymph node tissue, 28% to 81% in pleural fluid, 90% in pleural tissue, and 31% to 56% in CSF. Specificity ranged from 90% to 100% (Lewinsohn 2017).

Alternative molecular methods for DST include the commercial line-probe assays, GenoType MTBDR*plus* assay (MTBDR*plus,* Hain LifeScience, Nehren, Germany), and the Nipro NTM+MDRTB detection kit 2 (Nipro, Tokyo, Japan), which detect the presence of mutations associated with drug resistance to isoniazid and rifampicin (Nathavitharana 2017). MTBDR*plus* is the most widely studied line-probe assay. Advantages of line-probe assays are that they can provide a result for detection of tuberculosis and drug resistance in one to two days. Drawbacks are that line-probe assays are expensive and need to be used in intermediate and central laboratories (Unitaid 2017). The WHO recommends that for persons with a sputum smear-positive specimen or a cultured tuberculosis isolate, commercial molecular line-probe assays may be used as the initial test instead of phenotypic culture-based DST to detect resistance to rifampicin and isoniazid (conditional recommendation, moderate certainty in the evidence for the test's accuracy) (WHO Consolidated Guidelines (Module 3) 2020). Other molecular assays for detection of tuberculosis and resistance to rifampicin and isoniazid along with instruments are in development (Walzl 2018).

Alere Determine™ TB LAM Ag (AlereLAM) Alere Inc, (Waltham, USA) is a commercially-available point-of-care test for tuberculosis disease (pulmonary and extrapulmonary tuberculosis). The test detects lipoarabinomannan (LAM), a component of the bacterial cell wall, which is present in the urine of some people with tuberculosis. AlereLAM is performed by placing urine on one end of a test strip, with results appearing as a band on the strip if tuberculosis is present. The test is simple, requires no special equipment, and shows results in 25 minutes. This urine test has potential advantages over sputum-based testing due to ease of sample collection. The accuracy of urinary LAM detection is improved among people living with HIV with advanced immunosuppression (Bjerrum 2019). In two randomized trials, the use of Alere LAM in HIV-positive adult inpatients was shown to reduce mortality (Gupta-Wright 2018; Peter 2016). Based on evidence from the randomized trials and a Cochrane Review (Bjerrum 2019), the WHO currently recommends that AlereLAM should be used to assist in the diagnosis of active tuberculosis in HIV-positive adults, adolescents, and children (WHO Consolidated Guidelines (Module 3) 2020). The key change from the WHO 2015 guidelines is broadening the indication for use of LF-LAM among HIV-positive inpatients with signs and symptoms of active tuberculosis (pulmonary and extrapulmonary); the test is now recommended for all such patients, irrespective of their CD4 count. The full recommendations, which differ for inpatients and outpatients, are described here (WHO Consolidated Guidelines (Module 3) 2020).

Fujifilm SILVAMP TB LAM (FujiLAM, co-developed by Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland and Fujifilm, Tokyo, Japan) is a new, urine-based, point-of-care test for tuberculosis diagnosis in people living with HIV. In an individual participant data meta-analysis that included five cohorts of people living with HIV, FujiLAM was found to have superior sensitivity, 70.7% (95% CI 59.0% to 80.8%), compared to AlereLAM sensitivity of 42.3% (31.7% to 51.8%), against a microbiological reference standard; FujiLAM had lower specificity, 90.9% (87.2 to 93.7), compared to AlereLAM specificity of 95.3% (92.2 to 97.7) (Broger 2020). At the time of writing, additional prospective clinical trials of FujiLAM are ongoing to generate data for an updated WHO policy review.

Rationale

Xpert Ultra and Xpert MTB/RIF are rapid tests that may provide benefits for patients (earlier diagnosis and the opportunity to begin earlier, appropriate treatment), especially in high tuberculosis-burden countries.

Since 2010, the WHO has recommended the use of Xpert MTB/RIF as the preferred initial diagnostic test for people thought to have MDR-TB or HIV-associated tuberculosis (strong recommendation, moderate-certainty evidence) (WHO Xpert MTB/RIF Policy 2011). In 2013, the WHO expanded the recommendations, stating that Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected of having tuberculosis (conditional recommendation acknowledging

resource implications, high-quality evidence) (WHO Xpert MTB/RIF Policy Update 2013). The 2013 recommendations extended to the diagnosis of several forms of extrapulmonary tuberculosis, including tuberculous meningitis and lymph nodes and other tissue. In addition, the WHO recommended that following an Xpert MTB/RIF test that demonstrates rifampicin resistance, subsequent DST (e.g. using a line-probe assay to second-line drugs) remains essential to detect resistance to drugs other than rifampicin (WHO Xpert MTB/RIF Policy Update 2013). In 2017, based on a non-inferiority analysis of Xpert Ultra compared with Xpert MTB/RIF (Dorman 2018), the WHO stated that recommendations on the use of Xpert MTB/RIF also apply to the use of Xpert Ultra as the initial diagnostic test for all adults and children with signs and symptoms of tuberculosis (WHO Xpert Ultra 2017).

In December 2019, the WHO convened a Guideline Development Group to update the recommendations on the use of molecular assays intended as initial tests for the diagnosis of pulmonary and extrapulmonary tuberculosis and rifampicin resistance. To extend the work of our previous Cochane Review (Kohli 2018), we performed this review update to inform the WHO policy (WHO Consolidated Guidelines (Module 3) 2020).

The Background and Methods sections of this review include some text that overlaps with some of our other reviews for Xpert MTB/RIF Ultra and Xpert MTB/RIF for diagnosing tuberculosis (Horne 2019; Kay 2020; Shapiro 2020; Vonasek 2020).

OBJECTIVES

To estimate the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for a) extrapulmonary tuberculosis by site of disease and b) rifampicin resistance, in adults with presumptive extrapulmonary tuberculosis. Presumptive tuberculosis refers to a patient who presents with symptoms or signs suggestive of tuberculosis.

Secondary objectives

- To compare the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for a) extrapulmonary tuberculosis by site of disease, and b) rifampicin resistance.
- To investigate the effects of potential sources of heterogeneity on test accuracy across the included studies.

For potential sources of heterogeneity, for extrapulmonary tuberculosis, we included smear status, HIV status, and prevalence of extrapulmonary tuberculosis. For cerebrospinal fluid (CSF), we considered the presence of a concentration step and specimen volume.

For rifampicin resistance, we planned to assess the impact of the prevalence of rifampicin resistance on accuracy estimates, but we had insufficient data for this analysis.

METHODS

Criteria for considering studies for this review

Types of studies

We included cross-sectional and cohort studies. In addition, we had planned to include randomized controlled trials that evaluated the use of the index(s) test on patient health outcomes, but that also reported sensitivity and specificity. Although the study design was a randomized trial for the purpose of determining the impact of the test on participant outcomes, the study design was a cross-sectional study for the purpose of determining the diagnostic accuracy of the index tests in this review. However, we did not identify any randomized controlled trials. We used abstracts to identify published studies and included these when they met the inclusion criteria. We only included studies that reported data comparing the index test(s) to an acceptable reference standard from which we could extract true-positive (TP), true-negative (TN), false-positive (FP), and false-negative (FN) values. We excluded case-control studies and case reports.

Participants

We included studies where at least 85% of the participants enrolled were adults aged 15 years or older with presumptive extrapulmonary tuberculosis from all settings and countries. Restricting the age group to adults differs from the original review, where we also included children (Kohli 2018). We did this because children are now included in a separate Cochrane Review (Kay 2020). We excluded studies where we could not disaggregate data on adults from those in children and studies where we could not tell the age of the participants enrolled.

We included non-respiratory specimens (such as CSF, pleural fluid, lymph node aspirate or tissue). We excluded sputum and other respiratory specimens, such as fluid obtained from bronchial alveolar lavage and tracheal aspiration. As we anticipated finding many studies, we set a bar to exclude smaller studies to reduce unnecessary work. We therefore required studies to provide data for at least five specimens for a given form of extrapulmonary tuberculosis included in the review. We excluded studies evaluating the use of Xpert Ultra and Xpert MTB/RIF to diagnose relapse of previously-treated extrapulmonary tuberculosis, so as to avoid the selection bias that may arise by limiting to a group that is already at elevated risk of extrapulmonary tuberculosis. We attempted to identify studies that included participants who were not taking anti-tuberculosis drugs or had taken anti-tuberculosis drugs for less than seven days.

Index tests

The index tests were Xpert Ultra and Xpert MTB/RIF.

Index test results are automatically generated (i.e. there is a single threshold), and the user is provided with a printable test result as follows.

Xpert Ultra

- MTB (M tuberculosis) DETECTED HIGH; RIF (rifampicin) Resistance DETECTED
- MTB DETECTED MEDIUM; RIF Resistance DETECTED
- MTB DETECTED LOW; RIF Resistance DETECTED
- MTB DETECTED VERY LOW; RIF Resistance DETECTED
- MTB DETECTED HIGH; RIF Resistance NOT DETECTED
- MTB DETECTED MEDIUM; RIF Resistance NOT DETECTED
- MTB DETECTED LOW; RIF Resistance NOT DETECTED
- MTB DETECTED VERY LOW; RIF Resistance NOT DETECTED
- MTB DETECTED HIGH; RIF Resistance INDETERMINATE
- MTB DETECTED MEDIUM; RIF Resistance INDETERMINATE
- MTB DETECTED LOW; RIF Resistance INDETERMINATE

- MTB DETECTED VERY LOW; RIF Resistance INDETERMINATE
- MTB Trace DETECTED; RIF Resistance INDETERMINATE
- INVALID (the presence or absence of MTB cannot be determined)
- ERROR (the presence or absence of MTB cannot be determined)
- NO RESULT (the presence or absence of MTB cannot be determined)

Xpert Ultra incorporates a semi-quantitative classification for results: trace, very low, low, moderate, and high. 'Trace' corresponds to the lowest bacterial burden for detection of *M tuberculosis* (Chakravorty 2017). We considered a trace result to mean MTB (*M tuberculosis*) DETECTED. However, no rifampicin-resistance result was available for participants with trace results because the trace sample is always reported as 'INDETERMINATE' for rifampin resistance (Cepheid 2018).

Xpert MTB/RIF

- MTB (*M tuberculosis*) DETECTED; Rif (rifampicin) resistance DETECTED
- MTB DETECTED; Rif resistance NOT DETECTED
- MTB detected; Rif resistance INDETERMINATE
- MTB NOT DETECTED
- INVALID (the presence or absence of MTB cannot be determined)
- ERROR (the presence or absence of MTB cannot be determined)
- NO RESULT (the presence or absence of MTB cannot be determined)

Target conditions

The target conditions were extrapulmonary tuberculosis and rifampicin resistance. We included eight common forms of extrapulmonary tuberculosis and considered subcategories of the target condition as separate diagnostic classifications (CDC 2018; Sandgren 2013; Sharma 2004).

- Tuberculous meningitis.
- Pleural tuberculosis.
- Lymph node tuberculosis.
- Genitourinary tuberculosis.
- Bone or joint tuberculosis.
- Peritoneal tuberculosis.
- Pericardial tuberculosis.
- Disseminated tuberculosis.

Table 1 lists the forms of extrapulmonary tuberculosis and specimens used for diagnosis in the review. We excluded less common forms, such as cutaneous tuberculosis, ocular tuberculosis, female genital tuberculosis, and tuberculosis of the breast, ear, and paranasal sinuses (Sharma 2004).

Reference standards

Detection of extrapulmonary tuberculosis

We included two reference standards.

- Solid or liquid mycobacterial culture.
  * 'Tuberculosis' was defined as a positive *M tuberculosis* culture
  * 'Not tuberculosis' was defined as a negative *M tuberculosis* culture
- Composite reference standard.
  * 'Tuberculosis' was defined as a positive *M tuberculosis* culture or positive composite reference test.
  * 'Not tuberculosis' was defined as a negative *M tuberculosis* culture and a negative composite reference test.

The composite reference standard might be based on the results of microbiological tests, culture or NAAT other than Xpert Ultra and Xpert MTB/RIF; imaging studies; histology; and clinical characteristics, and include at least one component test that is positive, according to the definition of the primary study authors.

For pleural tuberculosis, we defined the composite reference standard as the presence of granulomatous inflammation or a positive culture. We proposed this definition because we found evidence to support including histopathological examination in the definition. Around 60% of patients undergoing pleural biopsy will show granulomatous inflammation (American Thoracic Society 2000). In a prospective cohort study of participants with clinical and radiological findings consistent with pleural tuberculosis, Conde 2003 found that histological examination of tissue obtained from pleural biopsy had a higher diagnostic yield (78%; 66/84) than that of culture (62%; 52/84).

Culture is considered the best reference standard for tuberculosis. However, culture may lead to misclassification of some cases of extrapulmonary tuberculosis as 'not tuberculosis', owing to the paucibacillary nature of the disease. This means that culture may have low sensitivity for extrapulmonary tuberculosis overall and further that culture sensitivity may differ for different forms of extrapulmonary tuberculosis (Lewinsohn 2017). This misclassification by culture may lead to biased estimates (overestimation or underestimation) of the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF. The extent of bias will depend on the frequency of errors by culture and the degree of correlation in errors by culture and the Xpert assays because culture and Xpert Ultra or Xpert MTB/RIF are likely to pick up cases with a higher bacterial load, and are likely to miss cases with a lower bacterial load. Ignoring this dependence could lead to an overestimation of the sensitivity of Xpert Ultra or Xpert MTB/RIF.

- Effect of low sensitivity of culture on Xpert sensitivity: the low sensitivity of culture means that index test FNs may be misclassified as TNs when culture is used as the reference standard. Therefore, when Xpert Ultra or Xpert MTB/RIF is evaluated against culture, the number of FNs (classified as negative by the index test and positive by the reference test) may be decreased and the sensitivity of the index test may be overestimated.
- Effect of low sensitivity of culture on Xpert specificity: the low sensitivity of culture means that index test TPs may be misclassified as FPs when culture is used as the reference standard. Therefore, when Xpert Ultra or Xpert MTB/RIF is evaluated against culture, the number of FPs (classified as positive by the index test and negative by the reference test) may be increased and specificity of the index test may be underestimated.

In contrast to culture, a composite reference standard that includes culture, other tests, and clinical characteristics may correctly classify index test results as TPs (instead of as FPs with respect to culture), especially in people with paucibacillary disease in whom culture may be negative. However, because of the uncertainties that surround a clinical diagnosis of tuberculosis and, in some instances, the conditional dependence of the index tests and other tests in the composite reference standard (for example, for most of these tests, detection of tuberculosis depends on bacillary load), a reference standard that uses additional tests and clinical characteristics (in culture-negative people) may incorrectly classify people without tuberculosis as having tuberculosis (Naaktgeboren 2013). An additional challenge with including a composite reference standard is that the definition of the composite reference standard may vary across studies, making it difficult to interpret the accuracy estimates.

Thus both reference standards, culture and composite, are imperfect and may affect accuracy estimates. In an attempt to improve the estimation of diagnostic accuracy, we applied a latent class meta-analysis model to the three most commonly studied forms of extrapulmonary tuberculosis. This approach provides the sensitivity and specificity of culture in addition to the accuracy of the index tests, thus adjusting for imperfect culture accuracy.

Detection of rifampicin resistance

The reference standard was culture-based DST using solid or liquid media or line-probe assays, as recommended by the WHO (WHO 2012; WHO Consolidated Guidelines (Module 3) 2020).

Search methods for identification of studies

We attempted to identify all relevant studies, regardless of language or publication status (published, unpublished, in press, or ongoing). We monitored abstracts to see if these studies were published during the time we performed the review. We included only published studies in the review.

Electronic searches

For the original review, we searched the literature on 7 August 2017. For this review update, we searched the literature on 2 August 2019 and again on 28 January 2020, specifically for studies of Xpert Ultra (studies could include Xpert Ultra alone or both Xpert Ultra and Xpert MTB/RIF), using the search terms and strategy described in Appendix 1. We searched the following databases:

- Cochrane Infectious Diseases Group Specialized Register;
- MEDLINE (OVID, from 1966);
- Embase (OVID, from 1974);
- Science Citation Index - Expanded (from 1900);
- Conference Proceedings Citation Index - Science (CPCI-S, from 1990);
- BIOSIS Previews (from 1926), all three from the Web of Science;
- Scopus (Elsevier, from 1970);
- Latin American Caribbean Health Sciences Literature (LILACS) (BIREME, from 1982).

We also searched ClinicalTrials.gov, the WHO International Clinical Trials Registry (ICTRP) Platform (www.who.int/trialsearch), and the International Standard Randomized Controlled Trials Number (ISRCTN) registry (www.isrctn.com/) for trials in progress, and ProQuest Dissertations & Theses A&I (www.proquest.com/pqdtglobal, from 1990) for dissertations.

To identify other systematic reviews and meta-analyses, we performed an additional search on 28 May 2020 in MEDLINE (PubMed), Embase (OVID), and the Cochrane Library, applying filters for systematic reviews (www.sign.ac.uk/search-filters.html) to search terms for Xpert and tuberculosis.

Searching other resources

We reviewed reference lists of included articles and any relevant review articles identified through the above methods. We also contacted researchers at FIND and other experts in the field of tuberculosis diagnostics for information on ongoing and unpublished studies.

Data collection and analysis

Selection of studies

We used Covidence to manage the selection of studies (Covidence 2017). Two review authors independently scrutinized titles and abstracts identified by electronic literature searching to identify potentially eligible studies. We selected any citation identified by either review author as potentially eligible for full-text review. The same review authors independently assessed full-text papers for study eligibility using predefined inclusion and exclusion criteria, and resolved any discrepancies by discussion. We recorded all studies excluded after full-text assessment and their reasons for exclusion in Characteristics of excluded studies. We illustrated the study selection process in a PRISMA diagram (Moher 2009).

Data extraction and management

Using a previously-developed form (Appendix 2), two review authors worked independently to extract data on the following characteristics.

- Author; publication year; country; setting (outpatient, inpatient, or both outpatient and inpatient); study design; manner of participant selection; number of participants enrolled; number of participants for whom results are available.
- Characteristics of participants: gender; age; HIV status; history of prior tuberculosis; receipt of anti-tuberculosis treatment.
- Index test.
- Target condition and subcategories.
- Type of reference standard.
- Quality Assessment of Studies of Diagnostic Accuracy - Revised (QUADAS-2) items.
- Details of specimen: type (such as CSF, pleural fluid, or lymph node aspirate or tissue); condition (fresh or frozen); smear-positive or smear-negative.
- Specimen preparation; homogenization step (for tissue specimens); concentration step and specimen volume (for CSF); adherence to WHO standard operating procedures.
- Number of TP, FP, FN, TN (i.e. true-positives, false-positives, false-negatives, and true-negatives), and trace results; number of inconclusive results for detection of extrapulmonary tuberculosis; number of indeterminate results for detection of rifampicin resistance.
- Number of missing or unavailable test results.

We classified country income status as either low- and middle-income or high-income, according to the World Bank List of Economies (World Bank 2020).

We extracted TP, FP, FN, and TN values for the following specimens: CSF, pleural fluid and tissue, lymph node aspirate and tissue (the latter specimen acquired by surgical biopsy), bone or joint aspirate and tissue, urine, peritoneal fluid and tissue, pericardial fluid and tissue, and blood. We extracted these values for each of the specimen types separately. For example, we used one 2 × 2 table for lymph node aspirate, and another 2 × 2 table for lymph node tissue. In situations in which a participant contributed more than one specimen but of different types, we extracted data for all specimens. When a study included data for both raw specimens and concentrated sediment involving the same participants, we preferentially extracted data for raw specimens, except in the case of CSF, for which we extracted data for concentrated sediment as recommended by the WHO (WHO 2014). We extracted accuracy data according to the defined reference standards (see Reference standards). We did not encounter any situations in which a subset of participants in a study received the reference standard but others did not. Hence, there was no need to make corrections for verification bias in the statistical analysis (Begg 1983).

In most studies, the number of specimens was the same as the number of participants. However, in some studies, the number of specimens exceeded the number of participants or study authors reported only the number of specimens. In the previous review (Kohli 2018), we added post hoc a sensitivity analysis limiting inclusion to studies that used one specimen per participant. In this review, we performed a similar sensitivity analysis for Xpert Ultra.

We contacted authors of primary studies for missing data or clarifications. We entered all data into Microsoft Excel 2014.

Assessment of methodological quality

We used the QUADAS-2 tool, tailored to this review, to assess the quality of the included studies (Appendix 3) (Whiting 2011). QUADAS-2 consists of four domains: patient selection, index test, reference standard, and flow and timing. We assessed all domains for risk of bias and the first three domains for concerns about applicability. Two review authors independently completed QUADAS-2 and resolved disagreements through discussion. We present the results of this quality assessment in text, tables, and graphs.

We followed Cochrane policy, which states that "authors of primary studies will not extract data from their own study or studies. Instead, another author will extract these data, and check the interpretation against the study report and any available study registration details or protocol".

Statistical analysis and data synthesis

We performed descriptive analyses of the characteristics of included studies using Stata 15 (Stata 2017), and we present key study characteristics in the Characteristics of included studies table. We used data reported in the TP, FP, FN, and TN format to calculate sensitivity and specificity estimates and 95% confidence intervals (CIs) for individual studies. We present individual study results graphically by plotting the estimates of sensitivity and specificity (and their 95% CIs) in forest plots and receiver operating characteristic (ROC) space using Review Manager 5 (RevMan 5) (RevMan 2014).

When data were sufficient, we performed meta-analyses to estimate pooled sensitivity and specificity and corresponding 95% credible interval (CrI, defined below) using an adaptation of the bivariate random-effects approach of Reitsma 2005, which uses the exact binomial likelihood for the observed proportions (Chu 2006). The bivariate random-effects approach allowed us to calculate the pooled estimates of sensitivity and specificity while dealing with potential sources of variation caused by (1) imprecision of sensitivity and specificity estimates within individual studies; (2) correlation between sensitivity and specificity across studies; and (3) variation in sensitivity and specificity between studies. The model has a hierarchical structure, with the logit sensitivity in individual studies assumed to come from a common probability distribution the mean of which is the pooled logit sensitivity, and the standard deviation is the between-study standard deviation, and likewise for the specificity. This structure allows for borrowing strength across studies. In the absence of sufficient studies, we simply present descriptive statistics. In addition, we determined predictive values at a pretest probability of 10%, a value suggested by the WHO.

We performed separate analyses grouped by type of extrapulmonary specimen (e.g. CSF, pleural fluid, peritoneal fluid) rather than determine summary accuracy estimates for all forms of extrapulmonary tuberculosis combined, because we considered the former approach to be most clinically meaningful. In addition, we performed separate analyses by reference standard.

Comparison of Xpert Ultra and Xpert MTB/RIF

We performed comparative meta-analyses by restricting the analyses to only those studies that made direct comparisons between Xpert Ultra and Xpert MTB/RIF within the same participants (Takwoingi 2013). We extracted the median and the 95% CrI for the difference in the pooled sensitivities and the difference in the pooled specificities, respectively, of Xpert Ultra versus Xpert MTB/RIF. We also calculated the probability that the difference exceeds zero in each case.

For analysis of Xpert MTB/RIF or Xpert Ultra accuracy for detection of rifampicin resistance, we include participants who (1) were culture-positive; (2) had a valid culture-based DST or line-probe assay (LPA) result; (3) were Xpert MTB/RIF or Xpert Ultra tuberculosis-positive; and (4) had a valid Xpert MTB/RIF or Xpert Ultra result for rifampicin resistance, detected or not detected (susceptible).

- Sensitivity = Xpert MTB/RIF (or Xpert Ultra) rifampicin resistance detected/phenotypic DST or LPA rifampicin-resistant.
- Specificity = Xpert MTB/RIF (or Xpert Ultra) rifampicin resistance not detected/phenotypic DST or LPA rifampicin-susceptible.

For detection of rifampicin resistance, when a study included multiple types of specimens, we based our determination of Xpert Ultra and Xpert MTB/RIF and sensitivity and specificity on all available data in the study, including data for specimens that we did not include in the primary analyses for detection of extrapulmonary tuberculosis. For example, if a study provided data for several specimen types combined (e.g. all tissue specimens) and we could not disaggregate the data for a specific specimen type, we included

all data (for all tissue specimens) in the analysis for rifampicin resistance detection. We did this because we did not expect the accuracy of Xpert Ultra or Xpert MTB/RIF for rifampicin resistance to vary by specimen type. We used the bivariate random-effects model to estimate pooled sensitivity and specificity.

We estimated all models using a Bayesian approach with low-information prior distributions using OpenBUGS software (Version 3.2.3) (Lunn 2009), along with R (R Core Team 2019). Under the Bayesian approach, all unknown parameters must be provided a prior distribution that defines the range of possible values of the parameter and the weight of each of those values, based on information external to the data. To allow observed data to dominate the final results, we chose to use low-information prior distributions. We defined prior distributions on the log-odds scale over the pooled sensitivity and specificity parameters, their corresponding between-study standard deviations, and the correlation between the sensitivities and specificities across studies. For the pooled log odds of the sensitivity or the pooled log odds of the specificity, we used a normal prior distribution with mean 0 and a wide variance of 4 (or a precision of 0.25). This corresponds to a roughly uniform distribution over the pooled sensitivity and pooled specificity on the probability scale. For the between-study precision, we used a gamma distribution with a shape parameter of 2 and a rate parameter of 0.5. This corresponds to a 95% prior CrI for the between-study standard deviation in the log odds of sensitivity or the log odds of specificity ranging from roughly 0.29 to 1.44, corresponding to moderate to high values of between-study heterogeneity. Covariance terms followed a uniform prior distribution whose upper and lower limits were determined by the sensitivity of the two tests. The OpenBUGS model used appears in Appendix 4. It is known that meta-analysis models can be sensitive to the choice of prior distributions over between-study standard deviation parameters. We therefore carried out sensitivity analyses and considered alternative prior distributions that are less informative, allowing a wider range of possible values. To study the sensitivity of all results to the choice of prior distributions given above, we considered alternative prior distributions that were less informative, allowing a wider range of possible values. We increased the variance of the normal distributions over the pooled log odds of sensitivity or specificity to 100. We used a uniform prior distribution ranging from 0 to 3 over the between-study standard deviation on the log odds scale (see programme in Appendix 4). We noted no appreciable change in pooled accuracy parameters but found that the posterior CrIs and prediction intervals were slightly wider, as expected.

We combined information from the prior distribution with the likelihood of the observed data, in accordance with Bayes' theorem, using the OpenBUGS programme, which provides a sample from the posterior distribution of each unknown parameter. We were particularly interested in the pooled sensitivity and specificity of Xpert and between-study variance in the sensitivity and specificity of Xpert on the log-odds scale. Using a sample from the posterior distribution, we calculated various descriptive statistics of interest. We estimated the median pooled sensitivity and specificity and their 95% CrI. The median or the 50% quantile is the value below which 50% of the posterior sample lies. We report the median because the posterior distributions of some parameters may be skewed and the median would be considered a better point estimate of the unknown parameter than the mean in such cases. The 95% CrI is the Bayesian equivalent of the classical (frequentist) 95% confidence interval (CI) (we will indicate 95% CI for individual study estimates and 95% CrI for pooled study estimates as appropriate). The 95% CrI may be interpreted as an interval that has a 95% probability of capturing the true value of the unknown parameter, given observed data and prior information. We prepared summary receiver operating characteristic (SROC) curves for each meta-analysis model, using the methods described in Harbord 2007.

We also determined the predicted sensitivity and specificity of Xpert MTB RIF and Xpert Ultra and their 95% CrIs. Predicted values represent our best guess for sensitivity and specificity in a future study and will be close to the pooled estimates. However, their CrIs may be different. If there is no heterogeneity at all between studies, the CrI around the predicted estimate will be the same as the CrI around the pooled estimate. On the other hand, if considerable heterogeneity is observed between studies, the CrI around the predicted estimate will be much wider than the CI around the pooled estimate.

In addition, we performed latent class analysis for three forms of extrapulmonary tuberculosis: tuberculous meningitis, pleural tuberculosis, and lymph node tuberculosis, using data from the two-by-two tables comparing the index test to culture as a reference standard. Latent class analysis is a statistical modelling technique that allows estimation of test accuracy in the absence of an adequate reference standard to define the presence or absence of disease (Van Smeden 2014). The latent class meta-analysis model expands the traditional meta-analysis model in two ways: (1) we added parameters for the sensitivity and specificity of culture; and (2) we added covariance terms to adjust for the dependence between the index test and culture among disease-positive and disease-negative participants in each study. We used hierarchical prior distributions over the logit sensitivity and logit specificity of culture. In other words, we assumed that the logit sensitivities in the individual studies come from a common probability distribution whose mean is the pooled mean logit sensitivity of culture and whose standard deviation is the between-study standard deviation. Likewise for the specificities. We used the same low-information prior distributions over the pooled logit mean and between-study standard deviation parameters as we had for the corresponding parameters for the index test. We used uniform prior distributions for covariance terms over their ranges, which are determined by the sensitivities and the specificities of the two tests in each study (see Appendix 4 for the OpenBUGS model). We found that we did not need to augment observed data with prior information from other sources for most models. However, in a post hoc analysis Xpert MTB/RIF in lymph node aspirate in which we suspected a systematic bias in the performance of culture, we used informative prior distributions over the specificity of culture (ranging from 99% to 100%) and the specificity of Xpert MTB/RIF (ranging from 98% to 100%) (see Appendix 4). We added the SROC plots of the latent class meta-analyses to the SROC plots resulting from the models in which culture was treated as a perfect test, so they could be compared.

Based on work evaluating Xpert MTB/RIF for childhood tuberculosis (Schumacher 2016), we anticipated that latent class meta-analyses would lead to a decrease in the estimated pooled sensitivity of Xpert Ultra and Xpert MTB/RIF and an increase in the estimated pooled specificity of Xpert Ultra and Xpert MTB/RIF compared with the primary analyses. In other words, this method should help to

correct the biases in Xpert Ultra and Xpert MTB/RIF sensitivity and specificity resulting from treating culture as a perfect reference standard, which we detailed earlier in the section on the reference standard.

Approach to inconclusive index test results

The proportion of inconclusive (non-determinate) rate for detection of pulmonary tuberculosis is the number of tests classified as 'invalid', 'error', or 'no result' divided by the total number of index tests performed. The proportion of inconclusive (indeterminate) rate for detection of rifampicin resistance is the number of tests classified as 'MTB DETECTED; Rif (rifampicin) resistance INDETERMINATE' divided by the total number of index test-positive results. For Xpert Ultra, we determined the proportion of inconclusive index test results = number of inconclusive test results divided by the total number of tests. In our previous review, we used a Bayesian hierarchical model for a single proportion to estimate the pooled proportion of inconclusive MTB/RIF test results (Kohli 2018). We reported these findings again in this review update. As we found very few inconclusive results reported, we excluded these results from the quantitative analysis.

Investigations of heterogeneity

Initially, we investigated heterogeneity through visual examination of forest plots of sensitivities and specificities and through visual examination of the ROC space of the raw data. When data allowed, we evaluated potential sources of heterogeneity using subgroup analyses and bivariate meta-regression. We included the following covariates.

- HIV status.
- For tuberculous meningitis, concentration step used for preparing specimen (yes or no).
- CSF specimen volume used for Xpert MTB/RIF or Xpert Ultra testing.

We had planned to investigate smear status, history of tuberculosis, and whether WHO standard procedures for preparing tissue specimens were followed. However, we had insufficient data to do this.

The impact of the prevalence of extrapulmonary tuberculosis on sensitivity and specificity is an important consideration. In a post hoc meta-regression analysis, for Xpert MTB/RIF we explored this question for CSF, pleural fluid, and lymph node aspirate. For Xpert Ultra we explored this question for CSF. We did not conduct other analyses, owing to an insufficient number of studies. For detection of rifampicin resistance, owing to a small number of studies, we could not assess the impact of prevalence of rifampicin resistance on accuracy estimates.

Nontuberculous mycobacteria

Nontuberculous mycobacteria (NTM), such as *M avium* complex and *M intracellulare*, constitute a multi-species group of human pathogens that are ubiquitous in water and soil. NTM can cause severe diseases that share clinical signs with tuberculosis but are treated differently. People living with HIV with severe immunosuppression are particularly vulnerable to infections caused by NTM (Gopinath 2010). Previous studies have shown that Xpert does not cross-react with other mycobacterial species (Blakemore 2010; Helb 2010). In our original review, we summarized data for NTM separately by determining the percentage of false-positive Xpert MTB/RIF results in specimens that grew NTMs (Kohli 2018). In this updated review, we therefore summarize data for NTM only for Xpert Ultra.

Sensitivity analyses

For Xpert Ultra testing in CSF, we performed sensitivity analyses to explore whether the overall findings were robust to potentially influential decisions. We did this by limiting inclusion in the meta-analysis to the following.

- Studies that used consecutive or random selection of participants.
- Studies in which the reference standard results were interpreted without knowledge of the index test results.
- Studies that included only one specimen per participant.

For Xpert Ultra, in CSF, we also planned to perform a sensitivity analysis by limiting studies to those that included only untreated participants. However, we were unable to confirm that studies met this criterion. We planned similar sensitivity analyses for pleural fluid and lymph node aspirate, but these analyses were not carried out owing to an insufficient number of studies. For all other specimen types, we had an insufficient number of studies for sensitivity analyses.

For Xpert MTB/RIF, in the original review we performed sensitivity analyses by type of extrapulmonary specimen and found that for most analyses, the sensitivity analyses made little difference to any of these findings (Kohli 2018). However, for Xpert MTB/RIF in CSF, in comparison with all studies, (sensitivity of 71.1% (60.9 to 80.4), and specificity of 98.0% (97.0 to 98.8)), studies that evaluated only one specimen per participant had lower pooled sensitivity at 63.5% (47.6 to 76.3) and lower pooled specificity at 96.1% (94.2 to 97.4).

Assessment of reporting bias

We did not perform a formal assessment of publication bias using methods such as funnel plots or regression tests because such techniques have not been helpful for diagnostic test accuracy studies (Macaskill 2010).

Summary of findings and assessment of the certainty of the evidence

We assessed the certainty of evidence using the GRADE approach for diagnostic studies (Balshem 2011; GRADEpro GDT 2015; Schünemann 2008; Schünemann 2016). As recommended, we rated the certainty of evidence as either high (not downgraded), moderate (downgraded by one level), low (downgraded by two levels), or very low (downgraded by more than two levels) based on five domains: risk of bias, indirectness, inconsistency, imprecision, and publication bias. For each outcome, the certainty of evidence started as high when there high-quality studies (cross-sectional or cohort studies) that enrolled participants with diagnostic uncertainty. If we found a reason for downgrading, we used our judgement to classify the reason as either serious (downgraded by one level) or very serious (downgraded by two levels).Two review authors discussed judgments and applied GRADE in the following way (Schünemann 2020a; Schünemann 2020b).

- *Assessment of risk of bias*. We used QUADAS-2 to assess risk of bias.

- *Indirectness*. We assessed indirectness in relation to the population (including disease spectrum), setting, interventions, and outcomes (accuracy measures). We also used prevalence as a guide to whether there was indirectness in the population.
- *Inconsistency*. GRADE recommends downgrading for unexplained inconsistency in sensitivity and specificity estimates. We carried out prespecified analyses to investigate potential sources of heterogeneity and downgraded when we could not explain inconsistency in the accuracy estimates.
- *Imprecision*. We considered a precise estimate to be one that would allow a clinically meaningful decision. We considered the width of the CrI (or CI) and asked, "Would we make a different decision if the lower or upper boundary of the CrI (or CI) represented the truth?" In addition, we worked out projected ranges for TP, FN, TN, and FP for a given prevalence of tuberculosis and made judgements on imprecision from these calculations.
- *Publication bias*. We rated publication bias as undetected (not serious) for several reasons: the comprehensiveness of the literature search and extensive outreach to tuberculosis researchers to identify studies; the presence only of studies that produced precise estimates of high accuracy despite small sample size; and our knowledge about studies that were conducted but not published.

For the 'Summary of findings' tables for CSF and pleural fluid, we provide evidence using culture as the reference standard, which is considered the best reference standard for tuberculosis (Lewinsohn 2017). For lymph node aspirate, we provide evidence using a composite reference because, based on findings from the original review (Kohli 2018), we believe a composite reference standard is preferable for estimating accuracy.

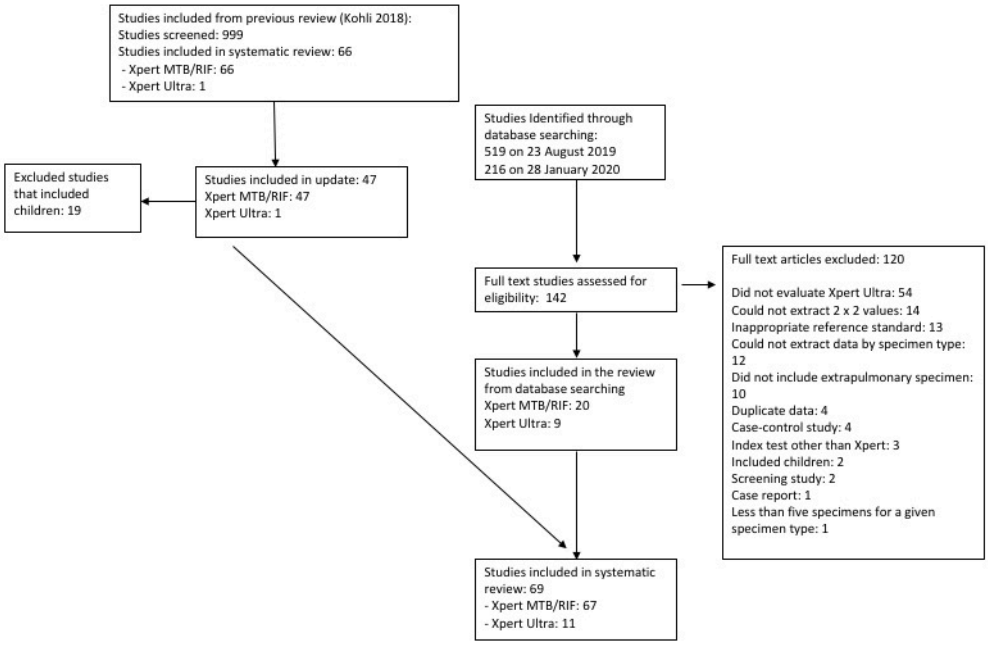
RESULTS

Results of the search

We identified and screened a total of 735 records for inclusion in this review update. Of these, we assessed 142 full-text papers against our inclusion criteria. We excluded 120 papers, mainly for the following reasons: study did not evaluate Xpert Ultra (n = 54); could not extract 2 x 2 values (n = 14); inappropriate reference standard (n = 13); could not extract data by specimen type (n = 12); did not include extrapulmonary specimen (n = 10): duplicate data (n = 4); case-control study (n = 4); index test other than Xpert MTB/RIF or Xpert Ultra (n = 3); study included children (n = 2); screening study (n = 2); case report (n = 1); and fewer than five specimens for a given specimen type (n = 1). From our previous review, we included 47 studies.
Thus, we included 69 unique studies that met the inclusion criteria in this review update.

Sixty-seven studies evaluated Xpert MTB/RIF (Ablanedo-Terrazas 2014; Ajbani 2018; Al-Ateah 2012; Azevedo 2018; Bahr 2015; Bahr 2017; Bera 2015; Biadglegne 2014; Blaich 2014; Causse 2011; Che 2017; Chen 2019; Chin 2019; Christopher 2013; Cresswell 2018; Cresswell 2020; Dhasmana 2014; Dhooria 2016; Donovan 2020; Du 2015; El-Din 2019; Feasey 2013; Friedrich 2011; Ghariani 2015; Gu 2015; Hanif 2011; Heemskerk 2018; Hillemann 2011; Iram 2015; Kim 2015a; Li 2017; Liang 2019; Ligthelm 2011; Lusiba 2014; Malbruny 2011; Meldau 2014; Meldau 2019; Metcalf 2018; Nataraj 2016; Nhu 2014; Ozkutuk 2014; Pandie 2014; Patel 2013; Peñata 2016; Rakotoarivelo 2018; Rufai 2015; Rufai 2017a; Rufai 2017b; Safianowska 2012; Sarfaraz 2018; Scott 2014; Sharma 2014; Sharma 2016; Sharma 2018; Siddiqi 2019; Sun 2019; Suzana 2016; Tadesse 2015; Trajman 2014; Ullah 2017; Vadwai 2011; Van Rie 2013; Wang 2019; Wang 2020; Wu 2019; Zeka 2011; Zmak 2013). Eleven studies evaluated Xpert Ultra. Of these 11 studies, nine evaluated both Xpert MTB/RIF and Xpert Ultra (Bahr 2017; Chin 2019; Cresswell 2020; Donovan 2020; Meldau 2019; Sun 2019; Wang 2019; Wang 2020; Wu 2019) and two studies evaluated Xpert Ultra alone (Antel 2020; Perez-Risco 2018). All studies but two (one in Spanish: Peñata 2016, and one in Turkish: Ozkutuk 2014), were written in English. Figure 2 shows the flow of studies in the review. We recorded the excluded studies, including those listed in the previous Cochrane Review (Kohli 2018) and the reasons for their exclusion in the Characteristics of excluded studies table.

Figure 2.



Methodological quality of included studies

Studies evaluating Xpert MTB/RIF and Xpert Ultra for detection of extrapulmonary tuberculosis

Figure 3 and Figure 4 show risk of bias and applicability concerns for each of the 69 studies included for tuberculosis detection. Risk of bias and applicability concerns are also presented specifically for studies evaluating Xpert Ultra and Xpert MTB/RIF for tuberculous meningitis (Appendix 5), pleural tuberculosis (Appendix 6), and lymph node tuberculosis (Appendix 7).

Figure 3. Risk of bias and applicability concerns graph for tuberculosis detection: review authors' judgements about each domain presented as percentages across included studies.

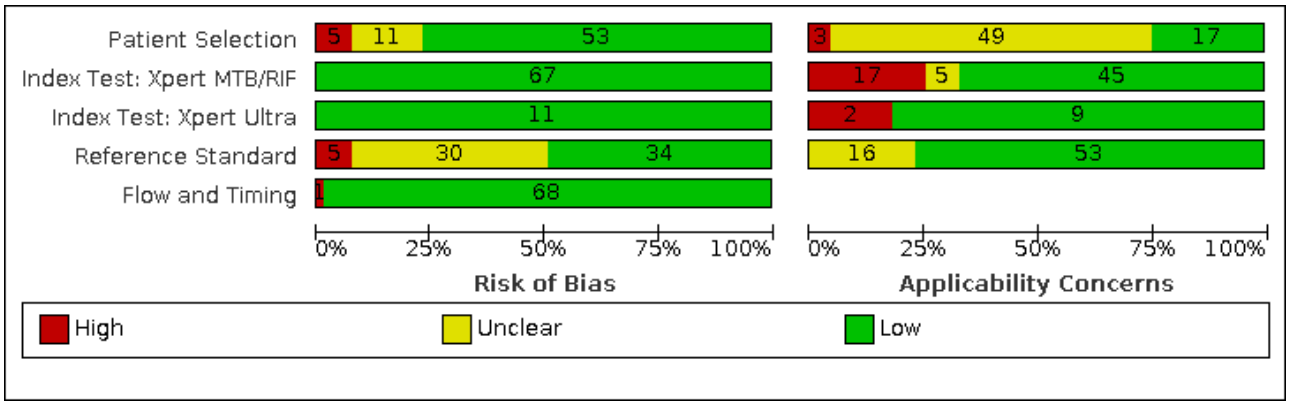


Figure 4. Risk of bias and applicability concerns summary for tuberculosis detection: review authors' judgements about each domain for each included study.

Figure 4. (Continued)

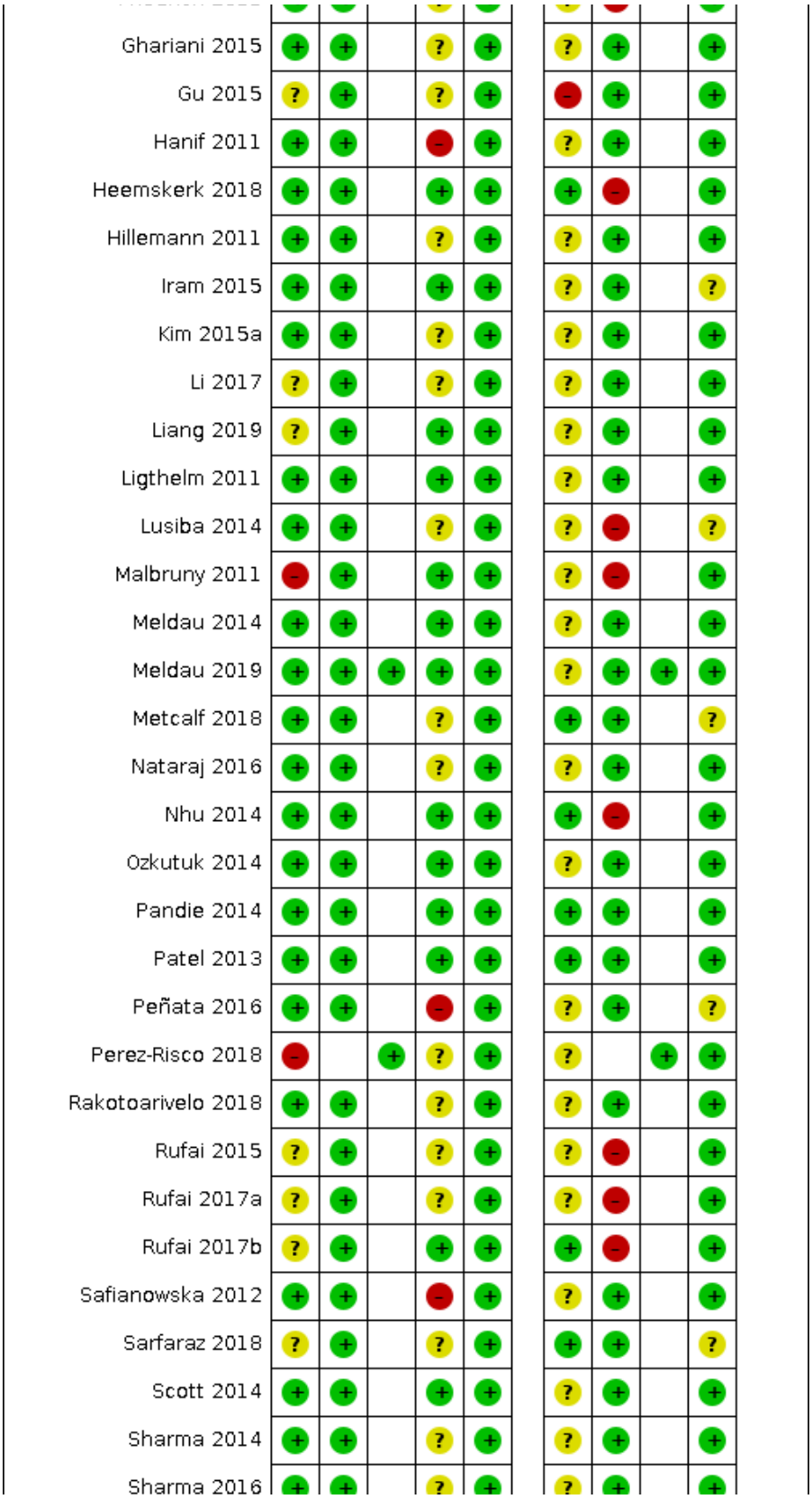
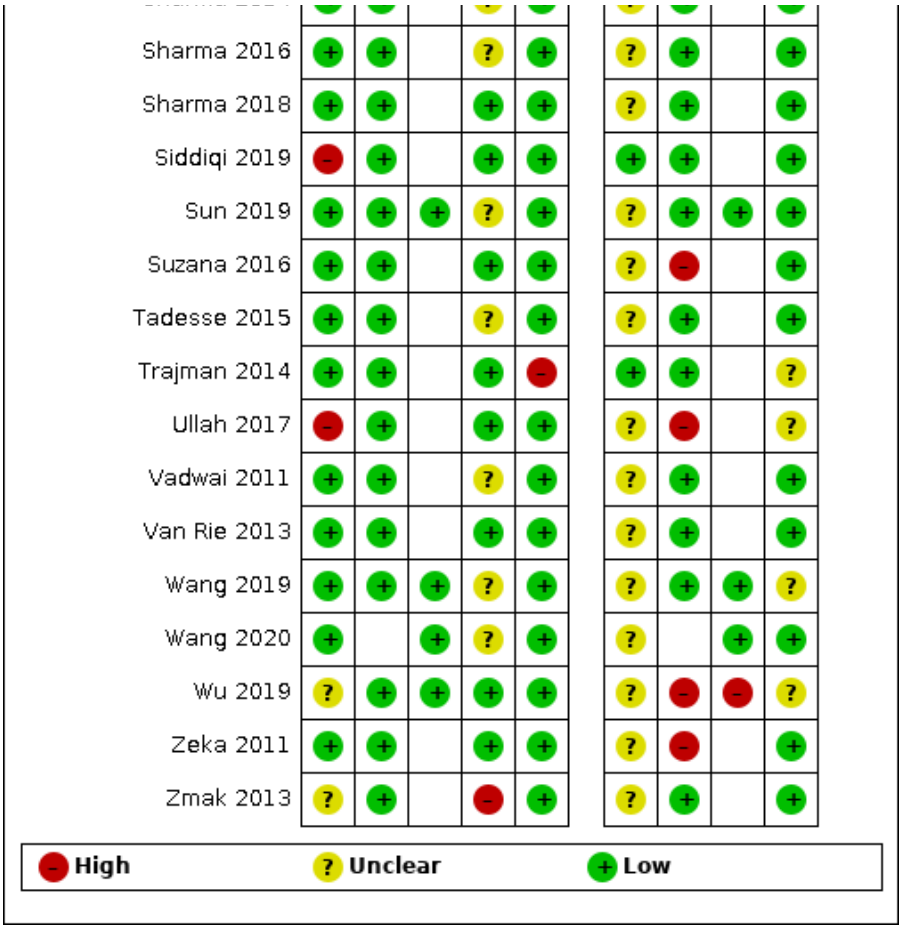


Figure 4. (Continued)



In the patient selection domain, we thought that 53 studies (77%) had low risk of bias, and five studies (7%) had high risk of bias for the following reasons: one study selected participants by convenience (Malbruny 2011) and four studies had inappropriate exclusions (Du 2015; Perez-Risco 2018; Siddiqi 2019; Ullah 2017). We thought that 11 studies (16%) had unclear risk of bias for the following reasons: the manner of patient selection was unclear in ten studies (Azevedo 2018; Gu 2015; Li 2017; Liang 2019; Rufai 2015; Rufai 2017a; Rufai 2017b; Sarfaraz 2018; Wu 2019; Zmak 2013), and it was unclear whether the study avoided inappropriate exclusions: one study (Bera 2015). Regarding applicability (patient characteristics and setting), we thought that 17 studies (25%) had low concern because participants were evaluated in local hospitals or primary health settings: three studies (Pandie 2014; Sarfaraz 2018; Trajman 2014), or in the case of tuberculous meningitis, tertiary centres: 14 studies (Ajbani 2018; Azevedo 2018; Bahr 2015; Bahr 2017; Chin 2019; Cresswell 2018; Cresswell 2020; Donovan 2020; Heemskerk 2018; Metcalf 2018; Nhu 2014; Patel 2013; Rufai 2017b Siddiqi 2019). Three studies (4%) had high concern because participants were evaluated exclusively as inpatients at a tertiary care centre (Che 2017; Du 2015; Gu 2015); and 52 (75%) studies had unclear or high concern because we could not tell the clinical setting or a high percentage of participants had received prior testing for tuberculosis (Antel 2020).

In the index test domain, we thought that all studies had low risk of bias because the results of the index tests (Xpert Ultra and Xpert MTB/RIF) are automatically generated, the user is provided with printable test results, and the test threshold is prespecified. Regarding applicability, with respect to Xpert Ultra, we thought that 9/11 studies (82%) had low risk of bias (Antel 2020; Bahr 2017; Cresswell 2020; Donovan 2020; Meldau 2019; Perez-Risco 2018; Sun 2019; Wang 2019; Wang 2020) and 2/11 studies (18%) had high risk of bias because the index test was not performed according to WHO standard operating procedures (Chin 2019; Wu 2019). With respect to Xpert MTB/RIF, we thought that 45/67 studies (67%) had low concern because at least 75% of the specimen types in these studies were processed according to WHO recommendations; 17/67 studies (25%) had high concern because fewer than 50% of the specimen types in these studies were processed according to WHO recommendations (Causse 2011; Che 2017; Chin 2019; Dhasmana 2014; Feasey 2013; Friedrich 2011; Heemskerk 2018; Lusiba 2014; Malbruny 2011; Nhu 2014; Rufai 2015; Rufai 2017a; Rufai 2017b; Suzana 2016; Ullah 2017; Wu 2019; Zeka 2011). We thought that 5/67 studies (7%) had unclear concern because either the manner of specimen processing was not reported (four studies: Ajbani 2018; Azevedo 2018; Bera 2015; Cresswell 2018), or only 50% of the specimen types were processed according to WHO recommendations (one study: Christopher 2013).

In the reference standard domain, 34 studies (49%) had low risk of bias because results of the reference standard were interpreted without knowledge of results of the index test and only non-sterile

specimens were decontaminated (Ajbani 2018; Antel 2020; Bahr 2015; Bahr 2017; Bera 2015; Che 2017; Chin 2019; Christopher 2013 ; Cresswell 2018; Cresswell 2020; Dhooria 2016; Donovan 2020; Feasey 2013; Heemskerk 2018; Iram 2015; Liang 2019; Ligthelm 2011; Malbruny 2011; Meldau 2014; Meldau 2019; Nhu 2014; Ozkutuk 2014; Pandie 2014; Patel 2013; Rufai 2017b; Scott 2014; Sharma 2018; Siddiqi 2019; Suzana 2016; Trajman 2014; Ullah 2017; Van Rie 2013; Wu 2019; Zeka 2011). Five studies (7%) had high risk of bias because results of the reference standard were interpreted with knowledge of results of the index test (Blaich 2014; Hanif 2011; Peñata 2016; Safianowska 2012; Zmak 2013). Thirty studies (43%) had unclear risk of bias for the following reasons: seven studies did not report whether there was blinding of the reference standard (Azevedo 2018; El-Din 2019; Lusiba 2014; Metcalf 2018; Perez-Risco 2018; Wang 2019; Wang 2020); 21 studies decontaminated specimens generally considered to be sterile (Al-Ateah 2012; Biadglegne 2014; Causse 2011; Chen 2019; Dhasmana 2014; Du 2015; Friedrich 2011; Ghariani 2015; Gu 2015; Hillemann 2011; Kim 2015a; Li 2017; Nataraj 2016; Rakotoarivelo 2018; Rufai 2015; Rufai 2017a; Sharma 2014; Sharma 2016; Sun 2019; Tadesse 2015; Vadwai 2011); and two studies did not report blinding and decontaminated specimens generally considered to be sterile (Ablanedo-Terrazas 2014; Sarfaraz 2018).

Regarding applicability of the reference standard, we thought that 53 studies (77%) had low concern because these studies performed a test to identify *M tuberculosis* species (speciation) and 16 studies (23%) had unclear concern because we could not tell whether the study performed speciation (Azevedo 2018; Bera 2015; Chin 2019; Christopher 2013; Cresswell 2018; Dhooria 2016; El-Din 2019; Iram 2015; Lusiba 2014; Metcalf 2018; Peñata 2016; Sarfaraz 2018; Trajman 2014; Ullah 2017; Wang 2019; Wu 2019).

In the flow and timing domain, we considered almost all studies to have low risk of bias, noting that all participants were accounted for in the analysis. One study included fewer than 50% of eligible participants in the analysis (Trajman 2014).

Studies evaluating Xpert Ultra for detection of rifampicin resistance

Figure 5 and Figure 6 show risk-of-bias and applicability concerns for each of the five studies included for rifampicin resistance detection.

Figure 5. Risk of bias and applicability concerns graph for rifampicin resistance detection in comparative studies of Xpert Ultra and Xpert MTB/RIF: review authors' judgements about each domain presented as percentages across included studies.

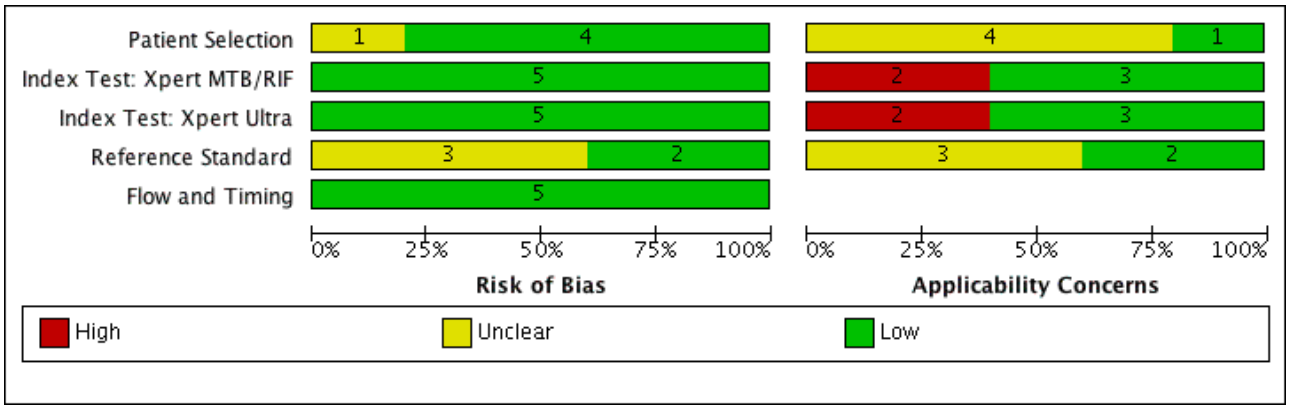
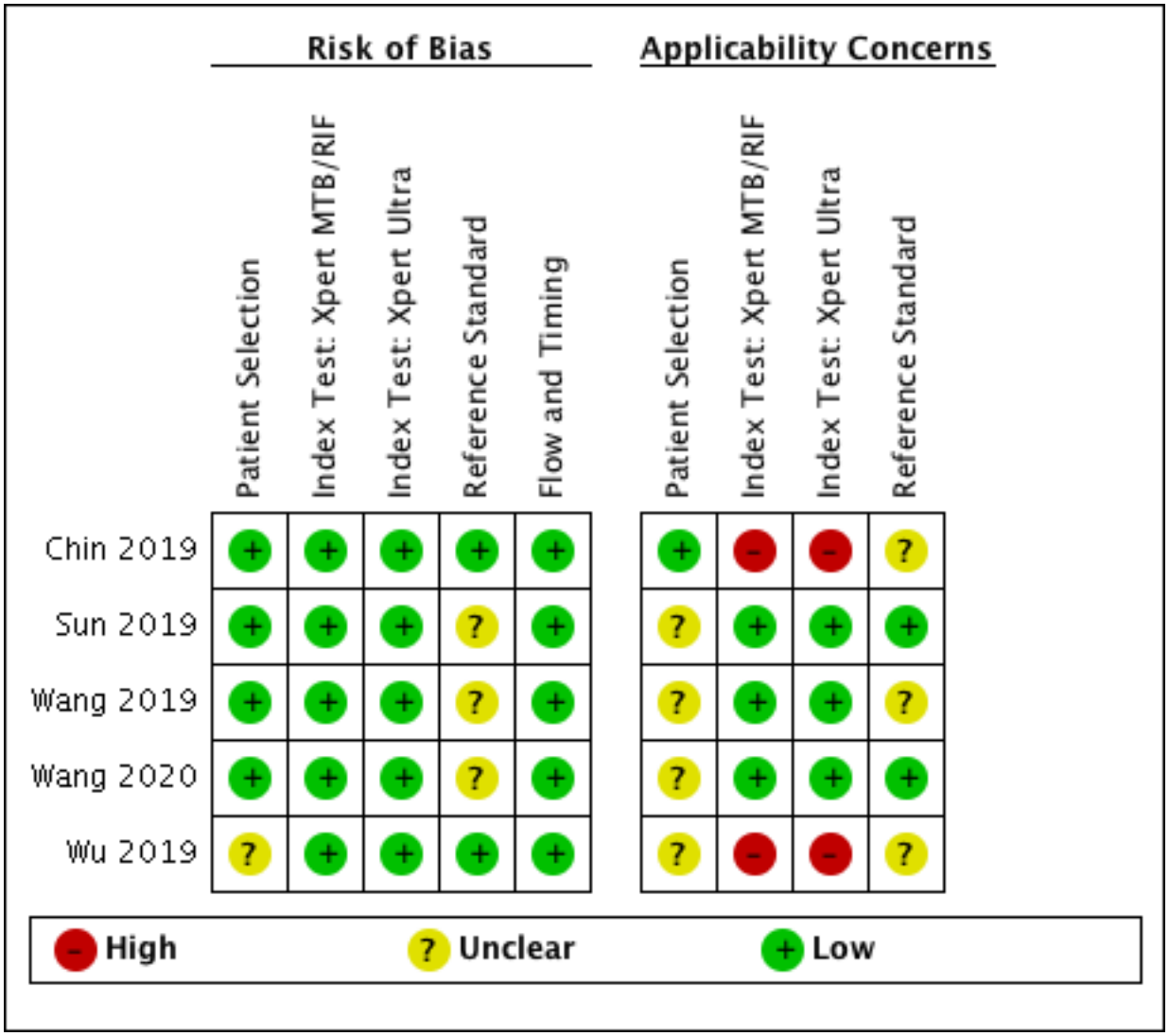


Figure 6. Risk of bias and applicability concerns summary for rifampicin resistance detection in comparative studies of Xpert Ultra and Xpert MTB/RIF: review authors' judgements about each domain for each included study.



In the patient selection domain, we thought that four studies (80%) had low risk of bias (Chin 2019; Sun 2019; Wang 2019; Wang 2020) and one study (20%) had unclear risk of bias as the manner of patient selection was unclear (Wu 2019). We thought that one study (20%) had low concern because participants were evaluated exclusively as inpatients at a tertiary care centre (Chin 2019) and four studies (80%) had unclear concern because we could not tell the details of the clinical setting (Sun 2019; Wang 2019; Wang 2020; Wu 2019).

In the index test domain, we thought that all studies had low risk of bias because the results of the index tests are automatically generated, the user is provided with printable test results, and the test threshold is prespecified. For applicability, with respect to Xpert Ultra, we thought that three studies (60%) had low concern because at least 75% of the specimen types in these studies were processed according to WHO recommendations (Sun 2019; Wang 2019; Wang 2020); two studies (40%) had high concern because fewer than 50% of the specimen types in these studies were processed according to WHO recommendations (Chin 2019; Wu 2019).

In the reference standard domain, two studies (40%) had low risk of bias because results of the reference standard were interpreted without knowledge of results of the index test and only non-sterile specimens were decontaminated (Chin 2019; Wu 2019). Three studies (60%) had unclear risk of bias as it was unclear whether blinding of the reference standard was performed (Sun 2019; Wang 2019; Wang 2020). For applicability of the reference standard, we thought that all studies had low concern because detection of rifampicin resistance occurs only when the *M tuberculosis* target is present within the specimen.

In the flow and timing domain, we considered all studies to have low risk of bias, noting that all participants were accounted for in the analysis.

Findings

The 69 studies were conducted in 28 different countries. Most of the studies were conducted in China (n = 10), India (n = 13), South Africa (n = 10), and Uganda (n = 6). Seven studies exclusively or mainly included HIV-positive participants (Ablanedo-Terrazas 2014; Azevedo 2018; Bahr 2015; Bahr 2017; Cresswell 2020; Feasey 2013; Van Rie 2013). Most studies performed the index tests and culture on the same specimen type, except for one study in which Xpert MTB/RIF was performed on blood and culture was performed on sputum (Feasey 2013). Most studies did not report the exact number of cultures used to confirm a diagnosis of tuberculosis, but it is likely that many studies used a single culture. We present key characteristics of the included studies in the Characteristics of included studies table.

I. Detection of extrapulmonary tuberculosis

Xpert Ultra: of the 11 studies, the number evaluating different specimens was as follows: tuberculous meningitis (CSF) six studies; pleural tuberculosis (pleural fluid) four studies; lymph node tuberculosis (lymph node aspirate) one study; genitourinary tuberculosis (urine) one study; bone or joint tuberculosis (bone or joint aspirate) two studies; and peritoneal tuberculosis (peritoneal fluid) one study.

Xpert MTB/RIF: of the 67 studies, the number of studies evaluating different specimens was as follows: tuberculous meningitis (CSF) 33 studies; pleural tuberculosis (fluid) 27 studies; lymph node tuberculosis (aspirate 15 studies, biopsy 11 studies); genitourinary tuberculosis (urine) 15 studies; bone or joint tuberculosis (aspirate 12 studies, tissue 3 studies); peritoneal tuberculosis (fluid 17 studies, tissue 1 study); pericardial tuberculosis (fluid 14 studies, tissue 2 studies); and disseminated tuberculosis (blood 2 studies). Several studies included more than one type of specimen.

Table 2 presents Xpert Ultra and Xpert MTB/RIF pooled sensitivity and specificity estimates and predictive values by reference standard for all forms of extrapulmonary tuberculosis and specimen types included in the review.

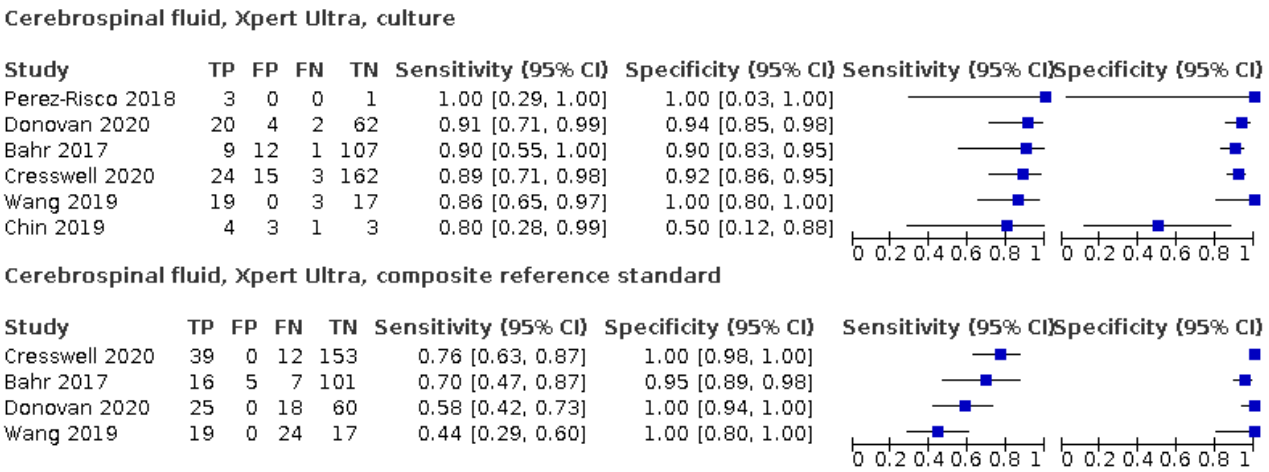
A: Xpert MTB/RIF and Xpert Ultra testing in cerebrospinal fluid for tuberculous meningitis

Xpert Ultra

Culture reference standard

Six studies evaluated Xpert Ultra in cerebrospinal fluid (CSF) specimens against culture (Bahr 2017; Chin 2019; Cresswell 2020; Donovan 2020; Perez-Risco 2018; Wang 2020). Xpert Ultra sensitivity ranged from 80% to 100% and specificity ranged from 50% to 100% (Figure 7). Chin 2019 reported the lowest specificity (50%). In this study, the investigators inoculated uncentrifuged CSF which could have led to lower culture positivity, thus resulting in a higher number of false positives. Perez-Risco 2018 (specificity 100%) contributed only one participant to this analysis. In CSF, Xpert Ultra pooled sensitivity and specificity (95% CrI) against culture were 89.4% (79.1 to 95.6) and 91.2% (83.2 to 95.7), (6 studies; 475 participants, 89 (18.7%) with tuberculosis); Table 2.

Figure 7. Forest plots of Xpert Ultra sensitivity and specificity in cerebrospinal fluid by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



Composite reference standard

In CSF, Xpert Ultra pooled sensitivity and specificity against a composite reference standard were 62.7% (45.7 to 77.0) and 99.1% (96.6 to 99.9), (4 studies; 496 participants); Table 2, Figure 7.

Latent class meta-analysis

We had insufficient data to obtain robust parameter estimates using the latent class model for Xpert Ultra in CSF.

Xpert MTB/RIF

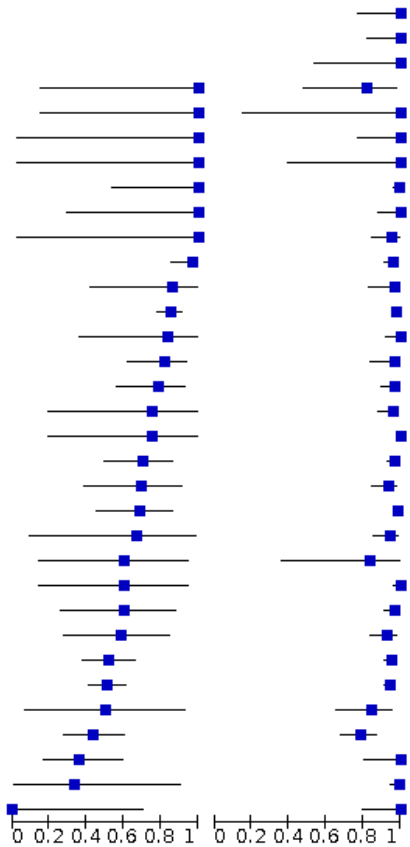
Culture reference standard

Thirty-three studies evaluated Xpert MTB/RIF in CSF specimens against culture (Ajbani 2018; Al-Ateah 2012; Azevedo 2018; Bahr 2015; Bahr 2017; Blaich 2014; Causse 2011; Chin 2019; Cresswell 2018; Cresswell 2020; Donovan 2020; Hanif 2011; Hillemann 2011; Kim 2015a; Li 2017; Malbruny 2011; Metcalf 2018; Nataraj 2016; Nhu 2014; Ozkutuk 2014; Patel 2013; Peñata 2016; Rakotoarivelo 2018; Rufai 2017b; Safianowska 2012; Sharma 2014; Siddiqi 2019; Suzana 2016; Ullah 2017; Vadwai 2011; Wang 2019; Zeka 2011; Zmak 2013). Xpert MTB/RIF sensitivity ranged from 0% to 100% and specificity ranged from 78% to 100% (Figure 8). For sensitivity, we thought that differences in CSF volume and processing could partly explain the heterogeneity. Three studies (Al-Ateah 2012; Hillemann 2011; Safianowska 2012) did not contribute data to the meta-analysis because sensitivity was not estimable.

Figure 8. Forest plots of Xpert MTB/RIF sensitivity and specificity in cerebrospinal fluid by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

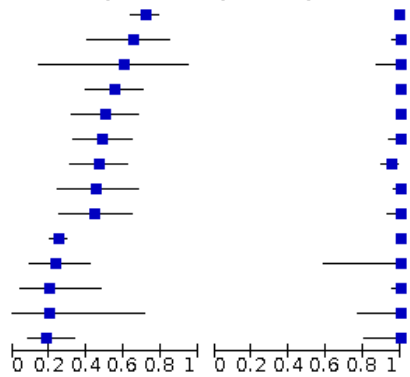
Cerebrospinal fluid, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	14	Not estimable	1.00 [0.77, 1.00]
Hillemann 2011	0	0	0	19	Not estimable	1.00 [0.82, 1.00]
Safianowska 2012	0	0	0	6	Not estimable	1.00 [0.54, 1.00]
Ajbani 2018	2	2	0	9	1.00 [0.16, 1.00]	0.82 [0.48, 0.98]
Blaich 2014	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Malbruny 2011	1	0	0	14	1.00 [0.03, 1.00]	1.00 [0.77, 1.00]
Hanif 2011	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Peñata 2016	6	1	0	148	1.00 [0.54, 1.00]	0.99 [0.96, 1.00]
Zeka 2011	3	0	0	28	1.00 [0.29, 1.00]	1.00 [0.88, 1.00]
Zmak 2013	1	2	0	43	1.00 [0.03, 1.00]	0.96 [0.85, 0.99]
Nataraj 2016	35	5	1	119	0.97 [0.85, 1.00]	0.96 [0.91, 0.99]
Metcalf 2018	6	1	1	29	0.86 [0.42, 1.00]	0.97 [0.83, 1.00]
Nhu 2014	103	6	18	252	0.85 [0.78, 0.91]	0.98 [0.95, 0.99]
Causse 2011	5	0	1	44	0.83 [0.36, 1.00]	1.00 [0.92, 1.00]
Patel 2013	22	1	5	31	0.81 [0.62, 0.94]	0.97 [0.84, 1.00]
Donovan 2020	18	2	5	63	0.78 [0.56, 0.93]	0.97 [0.89, 1.00]
Li 2017	3	3	1	67	0.75 [0.19, 0.99]	0.96 [0.88, 0.99]
Kim 2015a	3	0	1	250	0.75 [0.19, 0.99]	1.00 [0.99, 1.00]
Cresswell 2020	19	6	8	171	0.70 [0.50, 0.86]	0.97 [0.93, 0.99]
Rakotoarivelo 2018	9	4	4	60	0.69 [0.39, 0.91]	0.94 [0.85, 0.98]
Sharma 2014	15	3	7	205	0.68 [0.45, 0.86]	0.99 [0.96, 1.00]
Suzana 2016	2	3	1	53	0.67 [0.09, 0.99]	0.95 [0.85, 0.99]
Chin 2019	3	1	2	5	0.60 [0.15, 0.95]	0.83 [0.36, 1.00]
Azevedo 2018	3	0	2	96	0.60 [0.15, 0.95]	1.00 [0.96, 1.00]
Bahr 2017	6	4	4	115	0.60 [0.26, 0.88]	0.97 [0.92, 0.99]
Bahr 2015	7	5	5	63	0.58 [0.28, 0.85]	0.93 [0.84, 0.98]
Rufai 2017b	27	11	25	204	0.52 [0.38, 0.66]	0.95 [0.91, 0.97]
Siddiqi 2019	55	26	52	417	0.51 [0.42, 0.61]	0.94 [0.92, 0.96]
Ullah 2017	2	4	2	22	0.50 [0.07, 0.93]	0.85 [0.65, 0.96]
Cresswell 2018	17	17	22	62	0.44 [0.28, 0.60]	0.78 [0.68, 0.87]
Wang 2019	8	0	14	17	0.36 [0.17, 0.59]	1.00 [0.80, 1.00]
Ozkutuk 2014	1	1	2	107	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]
Vadwai 2011	0	0	3	16	0.00 [0.00, 0.71]	1.00 [0.79, 1.00]



Cerebrospinal fluid, Xpert MTB/RIF, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Nhu 2014	108	1	43	227	0.72 [0.64, 0.79]	1.00 [0.98, 1.00]
Bahr 2015	13	0	7	75	0.65 [0.41, 0.85]	1.00 [0.95, 1.00]
Zeka 2011	3	0	2	26	0.60 [0.15, 0.95]	1.00 [0.87, 1.00]
Cresswell 2020	25	0	20	159	0.56 [0.40, 0.70]	1.00 [0.98, 1.00]
Sharma 2014	17	0	17	176	0.50 [0.32, 0.68]	1.00 [0.98, 1.00]
Donovan 2020	21	0	22	59	0.49 [0.33, 0.65]	1.00 [0.94, 1.00]
Patel 2013	20	5	23	101	0.47 [0.31, 0.62]	0.95 [0.89, 0.98]
Bahr 2017	10	0	12	107	0.45 [0.24, 0.68]	1.00 [0.97, 1.00]
Rakotoarivelo 2018	12	0	15	50	0.44 [0.25, 0.65]	1.00 [0.93, 1.00]
Heemskerk 2018	95	0	284	231	0.25 [0.21, 0.30]	1.00 [0.98, 1.00]
Metcalf 2018	7	0	23	7	0.23 [0.10, 0.42]	1.00 [0.59, 1.00]
Azevedo 2018	3	0	12	86	0.20 [0.04, 0.48]	1.00 [0.96, 1.00]
Vadwai 2011	1	0	4	14	0.20 [0.01, 0.72]	1.00 [0.77, 1.00]
Wang 2019	8	0	35	17	0.19 [0.08, 0.33]	1.00 [0.80, 1.00]



In CSF, Xpert MTB/RIF pooled sensitivity and specificity (95% Crl) against culture were 71.1% (62.8 to 79.1) and 96.9% (95.4 to 98.0), respectively (30 studies; 3395 participants, 571 (16.8%) with tuberculosis); Table 2, Figure 8.

Composite reference standard

In CSF, Xpert MTB/RIF pooled sensitivity and specificity against a composite reference standard were 42.3% (32.1 to 52.8) and 99.8% (99.3 to 100.0), (14 studies; 2203 participants); Table 2, Figure 8.

Latent class meta-analysis

Based on the latent class meta-analysis model, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) for tuberculous meningitis were 74.7% (65.5 to 84.0) and 99.5% (99.1 to 99.7) (30 studies; 3395 participants); Table 3. The pooled sensitivity of culture at 80.8% (72.5 to 88.5) was estimated to be lower than 100%. The pooled specificity of culture was estimated to be 99.2% (98.7 to 99.5); Table 3.

Xpert Ultra versus Xpert MTB/RIF

In comparative accuracy studies evaluating both index tests, Xpert Ultra pooled sensitivity and specificity (95% CrI) against culture were 89.0% (77.9 to 95.2) and 91.0% (82.7 to 95.6) and Xpert MTB/RIF pooled sensitivity and specificity were 62.2% (43.7 to 78.1) and 96.8% (93.4 to 98.6), (5 studies; 471 participants), direct comparison, Table 2; Figure 9; Figure 10. For CSF, the difference between the sensitivities of Xpert Ultra and Xpert MTB/RIF was 26.2% (9.1 to 44.4). We estimated the probability that the pooled sensitivity of Xpert Ultra exceeds that of Xpert MTB/RIF was 0.997. The difference between the specificities of Xpert Ultra and Xpert MTB/RIF was −5.6% (−12.9 to −0.1). We estimated the probability that the pooled specificity of Xpert Ultra was less than that of Xpert MTB/RIF was 0.978; Table 4.

Figure 9. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in cerebrospinal fluid, comparative studies. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

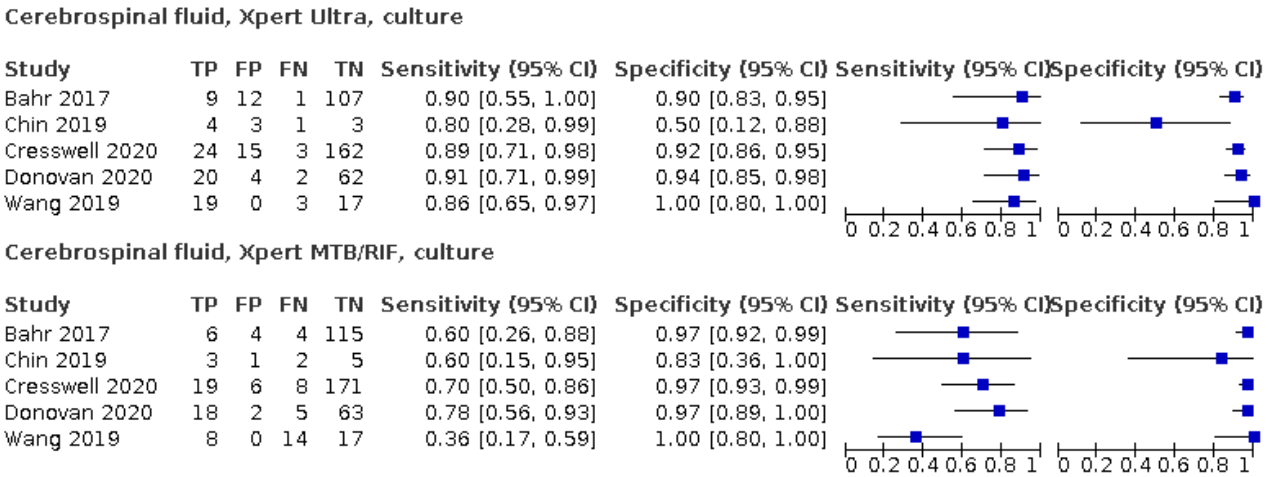
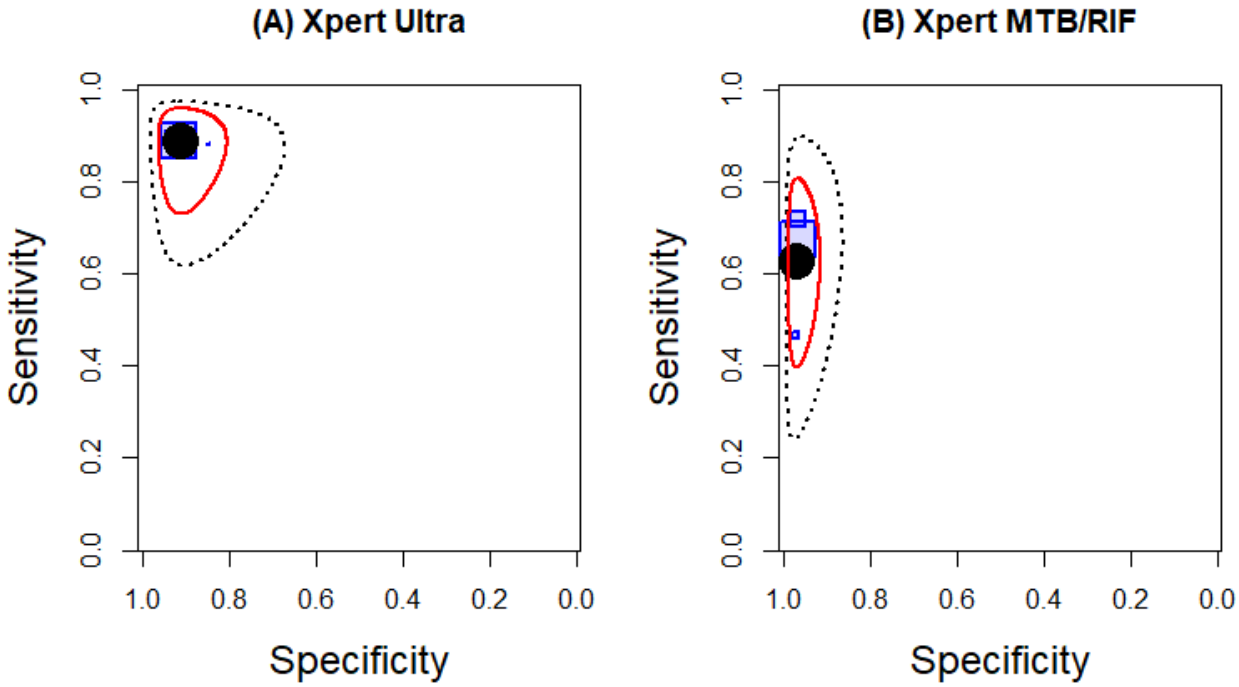


Figure 10. Summary plots of the sensitivity and specificity of Xpert Ultra (A) (5 studies) and Xpert MTB/RIF (B) (5 studies) in cerebrospinal fluid for detection of tuberculous meningitis. Each individual study is represented by a shaded square. The size of the square is proportional to the sample size of the study such that larger studies are represented by larger squares. The filled circle is the median pooled estimate for sensitivity and specificity. The solid curves represent the 95% credible region around the summary estimate; the dashed curves represent the 95% prediction region.

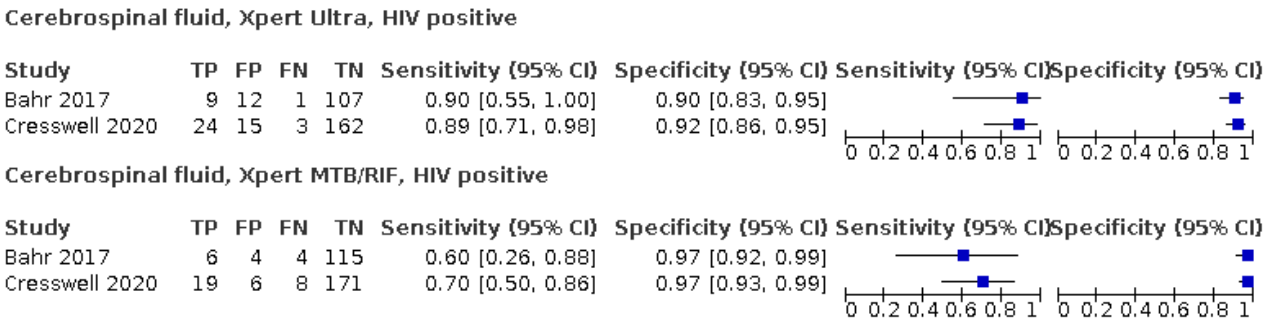


Investigations of heterogeneity

Xpert Ultra versus Xpert MTB/RIF testing in people living with HIV

We identified two studies that directly compared Xpert Ultra and Xpert MTB/RIF, both against culture, in people living with HIV. Sensitivity (95% CI) was 90% (55 to 100) (Bahr 2017) and 89% (71 to 98) (Cresswell 2020) for Xpert Ultra and 60% (26 to 88) (Bahr 2017) and 70% (50 to 86) (Cresswell 2020) for Xpert MTB/RIF. Specificity (95% CI) was 90% (83 to 95) (Bahr 2017) and 92% (86 to 95) (Cresswell 2020) for Xpert Ultra and 97% (95% CI 92 to 99) (Bahr 2017) and 97% (93 to 99) (Cresswell 2020) for Xpert MTB/RIF; Figure 11.

Figure 11. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in cerebrospinal fluid in HIV-positive people, with respect to culture. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive. .



Specimen concentration

Xpert Ultra

We found that concentrating CSF improved both Xpert Ultra sensitivity and specificity. Xpert Ultra pooled sensitivity in concentrated specimens was 90.5% (76.7 to 97.0) (3 studies; 421 participants) versus 88.4% (67.8 to 97.5) (3 studies; 54 participants) in unconcentrated specimens. Xpert Ultra pooled specificity in concentrated specimens was 91.9% (84.5 to 96.1) versus 88.6% (58.4 to 99.0) in unconcentrated specimens; Table 5. The probability that Xpert Ultra sensitivity and specificity are higher with concentrated CSF compared to unconcentrated CSF were 0.630 and 0.653, respectively.

Xpert MTB/RIF

We found that concentrating CSF improved both Xpert MTB/RIF sensitivity and specificity. Xpert MTB/RIF pooled sensitivity in concentrated specimens was 77.6% (67.2 to 85.9) (14, 2279 participants) versus 59.4% (48.3 to 70.5) (17,1123 participants) in unconcentrated specimens. Xpert MTB/RIF pooled specificity in concentrated specimens was 97.4% (96.1 to 98.4) versus 96.8% (94.0 to 98.7) in unconcentrated specimens, Table 5. The probability that Xpert MTB/RIF sensitivity and specificity are higher with concentrated CSF compared to unconcentrated CSF were 0.989 and 0.696, respectively.

Cerebrospinal fluid collection volumes

Xpert Ultra

Two studies reported the volume of CSF collected for Xpert Ultra testing, 3 mL in both studies. Sensitivities were similar: 90% (55 to 100) in Bahr 2017 and 89% (71 to 98) in Cresswell 2020. Specificities were also similar 90% (83 to 95) in Bahr 2017 and 92% (86 to 95) in Cresswell 2020.

Impact of tuberculosis prevalence on sensitivity and specificity

For Xpert Ultra, we found lower sensitivity in settings with higher tuberculosis prevalence (threshold 30%) than in those with lower tuberculosis prevalence: pooled sensitivity (95% CrI) of 88.3% (68.3 to 97.0) versus 90.8% (77.3 to 96.9). We found lower specificity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled specificity of 88.0% (64.3 to 97.9) versus 91.9% (82.5 to 96.6). In both analyses, the 95% CrIs overlapped; Table 6.

Similarly, for Xpert MTB/RIF, we found lower sensitivity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled sensitivity of 67.0% (49.0 to 81.5) versus 72.0% (62.4 to 81.2). We found lower specificity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled specificity of 94.1% (86.8 to 97.9) versus 97.3% (95.9 to 98.3). In both analyses, the 95% CrIs overlapped; Table 6. When we repeated the analysis at lower tuberculosis prevalence (threshold 10%), in the case of specificity, accuracy in the two groups was significantly different (probability of specificity being lower in the high tuberculosis prevalence group = 0.999); Table 6.

Sensitivity analyses

Overall, the sensitivity analyses made little difference to the findings; Table 7

Inconclusive Xpert Ultra and Xpert MTB/RIF results

Xpert Ultra

None of the studies evaluating Xpert Ultra for tuberculous meningitis reported this information.

Xpert MTB/RIF

We previously reported that for CSF, of 2096 tests performed, the pooled proportion of inconclusive Xpert MTB/RIF results was 0.9% (95% CrI 0.3 to 1.9) (Kohli 2018).

B: Xpert Ultra and Xpert MTB/RIF testing in pleural fluid for pleural tuberculosis

Xpert Ultra

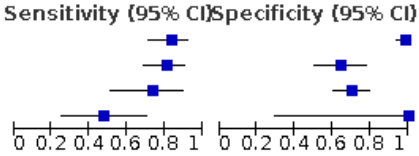
Culture reference standard

Four studies evaluated Xpert Ultra in pleural fluid with respect to culture (Perez-Risco 2018; Wang 2019; Wang 2020; Wu 2019). Xpert Ultra sensitivity ranged from 48% to 84% and specificity ranged from 65% to 100%; Figure 12.

Figure 12. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in pleural fluid and tissue by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

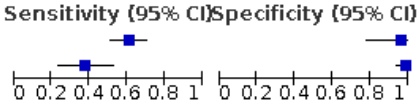
Pleural fluid, Xpert Ultra, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2020	46	1	9	83	0.84 [0.71, 0.92]	0.99 [0.94, 1.00]
Wang 2019	48	18	11	33	0.81 [0.69, 0.90]	0.65 [0.50, 0.78]
Wu 2019	17	30	6	72	0.74 [0.52, 0.90]	0.71 [0.61, 0.79]
Perez-Risco 2018	10	0	11	3	0.48 [0.26, 0.70]	1.00 [0.29, 1.00]



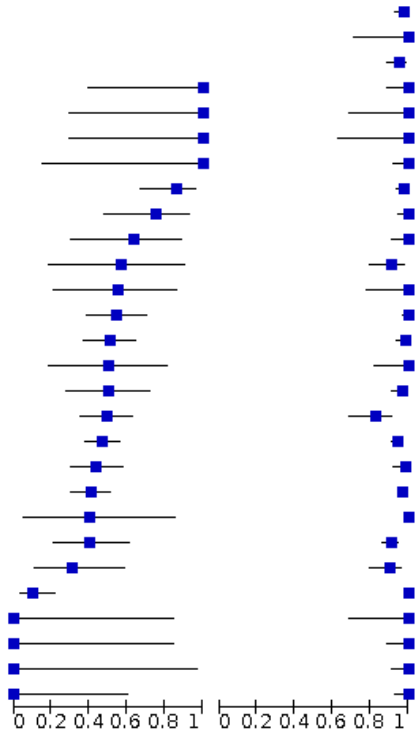
Pleural fluid, Xpert Ultra, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Wang 2019	66	1	42	22	0.61 [0.51, 0.70]	0.96 [0.78, 1.00]
Meldau 2019	18	1	30	83	0.38 [0.24, 0.53]	0.99 [0.94, 1.00]



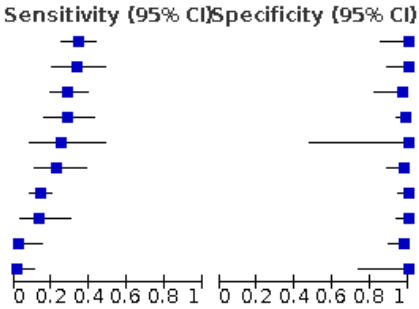
Pleural fluid, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hillemann 2011	0	2	0	103	Not estimable	0.98 [0.93, 1.00]
Iram 2015	0	0	0	11	Not estimable	1.00 [0.72, 1.00]
Christopher 2013	0	4	0	83	Not estimable	0.95 [0.89, 0.99]
Causse 2011	4	0	0	30	1.00 [0.40, 1.00]	1.00 [0.88, 1.00]
Al-Ateah 2012	3	0	0	10	1.00 [0.29, 1.00]	1.00 [0.69, 1.00]
Hanif 2011	3	0	0	8	1.00 [0.29, 1.00]	1.00 [0.63, 1.00]
Peñata 2016	2	0	0	46	1.00 [0.16, 1.00]	1.00 [0.92, 1.00]
Nataraj 2016	24	3	4	136	0.86 [0.67, 0.96]	0.98 [0.94, 1.00]
Che 2017	12	0	4	62	0.75 [0.48, 0.93]	1.00 [0.94, 1.00]
Rakotoarivelo 2018	7	0	4	39	0.64 [0.31, 0.89]	1.00 [0.91, 1.00]
Suzana 2016	4	4	3	42	0.57 [0.18, 0.90]	0.91 [0.79, 0.98]
Friedrich 2011	5	0	4	15	0.56 [0.21, 0.86]	1.00 [0.78, 1.00]
Rufai 2015	23	0	19	119	0.55 [0.39, 0.70]	1.00 [0.97, 1.00]
Wang 2020	28	1	27	83	0.51 [0.37, 0.65]	0.99 [0.94, 1.00]
Vadwai 2011	5	0	5	19	0.50 [0.19, 0.81]	1.00 [0.82, 1.00]
Wu 2019	11	3	11	94	0.50 [0.28, 0.72]	0.97 [0.91, 0.99]
Wang 2019	28	9	29	42	0.49 [0.36, 0.63]	0.82 [0.69, 0.92]
Scott 2014	59	21	66	336	0.47 [0.38, 0.56]	0.94 [0.91, 0.96]
Du 2015	24	1	31	70	0.44 [0.30, 0.58]	0.99 [0.92, 1.00]
Sharma 2014	37	8	54	265	0.41 [0.30, 0.51]	0.97 [0.94, 0.99]
Ozkutuk 2014	2	0	3	227	0.40 [0.05, 0.85]	1.00 [0.98, 1.00]
Li 2017	10	18	15	178	0.40 [0.21, 0.61]	0.91 [0.86, 0.94]
Meldau 2014	5	6	11	54	0.31 [0.11, 0.59]	0.90 [0.79, 0.96]
Kim 2015a	5	0	44	339	0.10 [0.03, 0.22]	1.00 [0.99, 1.00]
Malbruny 2011	0	0	2	10	0.00 [0.00, 0.84]	1.00 [0.69, 1.00]
Safianowska 2012	0	0	2	30	0.00 [0.00, 0.84]	1.00 [0.88, 1.00]
Zmak 2013	0	0	1	41	0.00 [0.00, 0.97]	1.00 [0.91, 1.00]
Zeka 2011	0	0	4	52	0.00 [0.00, 0.60]	1.00 [0.93, 1.00]



Pleural fluid, Xpert MTB/RIF, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Wu 2019	37	0	71	23	0.34 [0.25, 0.44]	1.00 [0.85, 1.00]
Sharma 2018	16	0	32	30	0.33 [0.20, 0.48]	1.00 [0.88, 1.00]
Lusiba 2014	25	1	62	28	0.29 [0.20, 0.39]	0.97 [0.82, 1.00]
Meldau 2019	14	1	35	83	0.29 [0.17, 0.43]	0.99 [0.94, 1.00]
Friedrich 2011	5	0	15	5	0.25 [0.09, 0.49]	1.00 [0.48, 1.00]
Meldau 2014	9	1	31	47	0.23 [0.11, 0.38]	0.98 [0.89, 1.00]
Liang 2019	22	0	133	64	0.14 [0.09, 0.21]	1.00 [0.94, 1.00]
Christopher 2013	4	0	26	61	0.13 [0.04, 0.31]	1.00 [0.94, 1.00]
Trajman 2014	1	1	32	51	0.03 [0.00, 0.16]	0.98 [0.90, 1.00]
El-Din 2019	1	0	45	12	0.02 [0.00, 0.12]	1.00 [0.74, 1.00]



Pleural tissue, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Suzana 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Du 2015	47	2	8	69	0.85 [0.73, 0.94]	0.97 [0.90, 1.00]

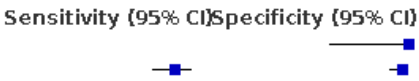
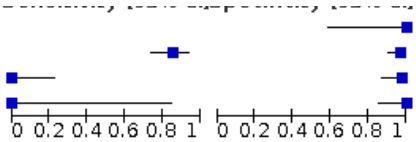


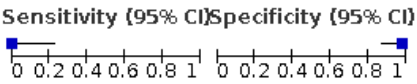
Figure 12. (Continued)

Suzana 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Du 2015	47	2	8	69	0.85 [0.73, 0.94]	0.97 [0.90, 1.00]
Christopher 2013	0	1	14	40	0.00 [0.00, 0.23]	0.98 [0.87, 1.00]
Ozkutuk 2014	0	0	2	24	0.00 [0.00, 0.84]	1.00 [0.86, 1.00]



Pleural tissue, Xpert MTB/RIF, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christopher 2013	0	1	14	40	0.00 [0.00, 0.23]	0.98 [0.87, 1.00]



In pleural fluid, Xpert Ultra pooled sensitivity and specificity against culture were 75.0% (58.0 to 86.4) and 87.0% (63.1 to 97.9), (4 studies; 398 participants, 158 (39.7%) with tuberculosis); Table 2; Appendix 8.

Composite reference standard

Two studies evaluated Xpert Ultra in pleural fluid with respect to a composite reference standard (Meldau 2019; Wang 2019); Figure 12; Appendix 8. Sensitivity ranged from 38% to 61%, and specificity ranged from 96% to 99%. We could not explain the variability in the sensitivity estimates and did not perform a meta-analysis.

Latent class meta-analysis

We had insufficient data to obtain robust parameter estimates using the latent class model for Xpert Ultra in pleural fluid.

Xpert MTB/RIF

Culture reference standard

Twenty-eight studies evaluated Xpert MTB/RIF in pleural fluid with respect to culture (Al-Ateah 2012; Causse 2011; Che 2017; Christopher 2013; Du 2015; Friedrich 2011; Hanif 2011; Hillemann 2011; Iram 2015; Kim 2015a; Li 2017; Malbruny 2011; Meldau 2014; Nataraj 2016; Ozkutuk 2014; Peñata 2016; Rakotoarivelo 2018; Rufai 2015; Safianowska 2012; Scott 2014; Sharma 2014; Suzana 2016; Vadwai 2011; Wang 2019; Wang 2020; Wu 2019; Zeka 2011; Zmak 2013). Xpert MTB/RIF sensitivity ranged from 0% to 100% and specificity ranged from 82% to 100% (Figure 12). Three studies (Christopher 2013; Hillemann 2011; Iram 2015) did not contribute data to the meta-analysis because sensitivity was not estimable.

In pleural fluid, Xpert MTB/RIF pooled sensitivity and specificity against culture were 49.5% (39.8 to 59.9) and 98.9% (97.6 to 99.7) (25 studies; 3065 participants, 644 (21.0%) with tuberculosis); Table 2; Appendix 8.

Composite reference standard

In pleural fluid, Xpert MTB/RIF pooled sensitivity and specificity against a composite reference standard were 18.9% (11.5 to 27.9) and 99.3% (98.1 to 99.8), (10 studies; 1024 participants) Table 2; Figure 12.

Latent class meta-analysis

Based on the latent class meta-analysis model, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) in pleural fluid were 53.1% (42.8 to 64.1) and 99.6% (99.3 to 99.8) (25 studies; 3065 participants) Table 3. Xpert MTB/RIF pooled sensitivity was slightly higher and its pooled specificity comparable to what was obtained when culture was treated as having perfect accuracy, with pooled sensitivity of 49.5% (39.8 to 59.9) and pooled specificity of 98.8% (97.6 to 99.7). The pooled sensitivity of culture at 89.5% (80.5 to 96.3) was estimated to be lower than 100%. The pooled specificity of culture was estimated to be 99.0% (98.2 to 99.5).

Xpert Ultra versus Xpert MTB/RIF

We had insufficient data for this analysis.

Impact of tuberculosis prevalence on sensitivity and specificity

For Xpert Ultra, we had insufficient data for this analysis.

For Xpert MTB/RIF, we found higher sensitivity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled sensitivity (95% CrI) of 20.7% (11.2 to 33.7) versus 15.5% (6.5 to 30.1). We found similar specificity in settings with higher tuberculosis prevalence and in those with lower tuberculosis prevalence: pooled specificity of 99.6% (97.9 to 99.9) versus 99.0% (96.9 to 99.8). In both analyses, the 95% CrIs overlapped; Table 6.

Sensitivity analyses

For Xpert Ultra, we had insufficient data for these analyses.

Inconclusive Xpert Ultra and Xpert MTB/RIF results

Xpert Ultra

Of the total 1013 tests performed, the percentage of inconclusive Xpert Ultra results was 0.3%. Only one study reported this information (Wang 2019).

Xpert MTB/RIF

We previously reported that for pleural fluid, of 1416 tests performed the pooled proportion of inconclusive Xpert MTB/RIF results was 1.2% (95% CrI 0.4 to 2.6) (Kohli 2018).

C: Xpert Ultra and Xpert MTB/RIF testing in pleural tissue for pleural tuberculosis

Xpert Ultra

Culture reference standard

We did not identify any studies evaluating Xpert Ultra in pleural tissue against culture.

Composite reference standard

We did not identify any studies evaluating Xpert Ultra in pleural tissue against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Four studies evaluated Xpert MTB/RIF in pleural tissue with respect to culture (Christopher 2013; Du 2015; Ozkutuk 2014; Suzana 2016). Xpert MTB/RIF sensitivity ranged from 0% to 85% and specificity ranged from 97% to 100%; Figure 12. One study reported zero tuberculosis cases (Suzana 2016). We did not perform a meta-analysis.

Composite reference standard

In pleural tissue, Xpert MTB/RIF sensitivity and specificity against a composite reference standard were 0% (0 to 23) and 98% (87 to 100) (1 study; 55 participants; Christopher 2013); Figure 12.

D: Xpert MTB/RIF and Xpert Ultra testing in lymph node aspirate for lymph node tuberculosis

Xpert Ultra

Culture reference standard

In lymph node aspirates, Xpert Ultra sensitivity and specificity against culture were 78% (40 to 97) and 78% (66 to 87), (1 study; 73 participants; 9 (12.3%) with tuberculosis; Antel 2020); Figure 13.

Figure 13. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in lymph node aspirate by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

Lymph node aspirate, Xpert Ultra, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	7	14	2	50	0.78 [0.40, 0.97]	0.78 [0.66, 0.87]

Lymph node aspirate, Xpert Ultra, composite reference standard

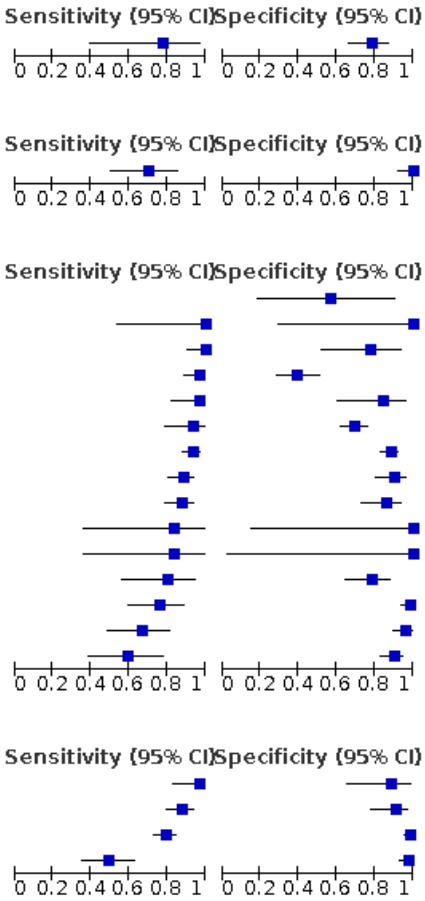
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	21	0	9	43	0.70 [0.51, 0.85]	1.00 [0.92, 1.00]

Lymph node aspirate, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kim 2015a	0	3	0	4	Not estimable	0.57 [0.18, 0.90]
Hanif 2011	6	0	0	3	1.00 [0.54, 1.00]	1.00 [0.29, 1.00]
Ullah 2017	36	4	0	14	1.00 [0.90, 1.00]	0.78 [0.52, 0.94]
Ghariani 2015	58	48	2	31	0.97 [0.88, 1.00]	0.39 [0.28, 0.51]
Ligthelm 2011	28	3	1	16	0.97 [0.82, 1.00]	0.84 [0.60, 0.97]
Biadglegne 2014	29	56	2	126	0.94 [0.79, 0.99]	0.69 [0.62, 0.76]
Van Rie 2013	139	23	10	172	0.93 [0.88, 0.97]	0.88 [0.83, 0.92]
Sharma 2014	85	7	11	63	0.89 [0.80, 0.94]	0.90 [0.80, 0.96]
Tadesse 2015	76	7	11	42	0.87 [0.79, 0.94]	0.86 [0.73, 0.94]
Al-Ateah 2012	5	0	1	2	0.83 [0.36, 1.00]	1.00 [0.16, 1.00]
Blaich 2014	5	0	1	1	0.83 [0.36, 1.00]	1.00 [0.03, 1.00]
Scott 2014	16	12	4	43	0.80 [0.56, 0.94]	0.78 [0.65, 0.88]
Nataraj 2016	29	1	9	87	0.76 [0.60, 0.89]	0.99 [0.94, 1.00]
Dhasmana 2014	24	3	12	77	0.67 [0.49, 0.81]	0.96 [0.89, 0.99]
Dhooria 2016	16	12	11	108	0.59 [0.39, 0.78]	0.90 [0.83, 0.95]

Lymph node aspirate, Xpert MTB/RIF, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ligthelm 2011	29	2	1	16	0.97 [0.83, 1.00]	0.89 [0.65, 0.99]
Tadesse 2015	81	4	11	40	0.88 [0.80, 0.94]	0.91 [0.78, 0.97]
Van Rie 2013	160	2	42	144	0.79 [0.73, 0.85]	0.99 [0.95, 1.00]
Dhooria 2016	26	2	27	92	0.49 [0.35, 0.63]	0.98 [0.93, 1.00]



Composite reference standard

In lymph node aspirates, Xpert Ultra sensitivity and specificity against a composite reference standard were 70% (51 to 85) and 100% (92 to 100), (1 study; 73 participants; 9 (12.3%) with tuberculosis; Antel 2020); Figure 13. Of note, with a composite reference standard, specificity was higher (100%) than that observed when using culture as the reference standard (78%).

Latent class meta-analysis

We had insufficient data to obtain robust parameter estimates using the latent class model for Xpert Ultra in lymph node aspirate.

Xpert MTB/RIF

Culture reference standard

Fifteen studies evaluated Xpert MTB/RIF in lymph node aspirates with for culture (Al-Ateah 2012; Biadglegne 2014; Blaich 2014; Dhasmana 2014; Dhooria 2016; Ghariani 2015; Hanif 2011; Kim 2015a; Ligthelm 2011; Nataraj 2016; Scott 2014; Sharma 2014; Tadesse 2015; Ullah 2017; Van Rie 2013). Xpert MTB/RIF sensitivity ranged from 59% to 100% and specificity from 57% to 100%; Figure 13. Xpert MTB/RIF specificity in lymph node aspirates was considerably more heterogeneous than in CSF and pleural fluid. The variability in Xpert MTB/RIF specificity in lymph node aspirates was unexpected and may be the result of a systematic, unexplained bias in some studies. One study did not contribute data to the meta-analysis because sensitivity was not estimable (Kim 2015a).

In lymph node aspirates, Xpert MTB/RIF pooled sensitivity and specificity against culture were 88.9% (82.7 to 93.6) and 86.2% (78.0 to 92.3) (14 studies; 1588 participants, 627 (39.5%) with tuberculosis); Table 2.

Composite reference standard

In lymph node aspirates, Xpert MTB/RIF pooled sensitivity and specificity against a composite reference standard were 81.6% (61.9 to 93.3) and 96.4% (91.3 to 98.6), (4 studies; 679 participants); Table 2; Figure 13. Of note, with a composite reference standard, specificity was less variable and pooled specificity higher than that observed when using culture as the reference standard (86.0%).

Latent class meta-analysis

Based on the latent class meta-analysis model, Xpert MTB/RIF pooled sensitivity and specificity (95% CrI) in lymph node aspirate were 91.3% (84.9 to 96.3) and 99.5% (99.1 to 99.7) (14 studies; 1588 participants); Table 3. Xpert MTB/RIF pooled sensitivity and pooled specificity were higher than when culture was treated as having perfect accuracy, with pooled sensitivity of 88.9% (82.7 to 93.6) and pooled specificity of 86.2% (78.0 to 92.3). The pooled sensitivity of culture at 84.9% (74.0 to 92.8) was estimated to be lower than 100%. The pooled specificity of culture was estimated to be 98.8% (97.7 to 99.4); Table 3. The latent class meta-analysis resulted in high precision in the specificity of Xpert MTB/RIF across studies. This was the result of adjustments for the imperfect and heterogeneous accuracy of culture across studies.

Xpert Ultra versus Xpert MTB/RIF

We had insufficient data for this analysis.

Impact of tuberculosis prevalence on sensitivity and specificity

For Xpert Ultra, we had insufficient data for this analysis.

For Xpert MTB/RIF, we found higher sensitivity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled sensitivity (95% CrI) of 93.1% (88.9 to 96.3) versus 72.2% (64.9 to 87.2). We found lower specificity in settings with higher tuberculosis prevalence than in those with lower tuberculosis prevalence: pooled specificity of 83.2% (69.5 to 92.1) versus 90.0% (78.3 to 95.9). In the case of sensitivity, accuracy in the two groups was significantly different (probability of sensitivity being lower in the high tuberculosis prevalence group = 0.999); Table 6.

Sensitivity analyses

For Xpert Ultra, we had insufficient data for these analyses.

Inconclusive Xpert MTB/RIF and Xpert Ultra results

Xpert Ultra

None of the studies reported this information.

Xpert MTB/RIF

We previously reported that for lymph node aspirates, in the 1134 tests performed, the pooled proportion of inconclusive Xpert MTB/RIF results was 1.0% (95% CrI 0.4 to 2.0) (Kohli 2018).

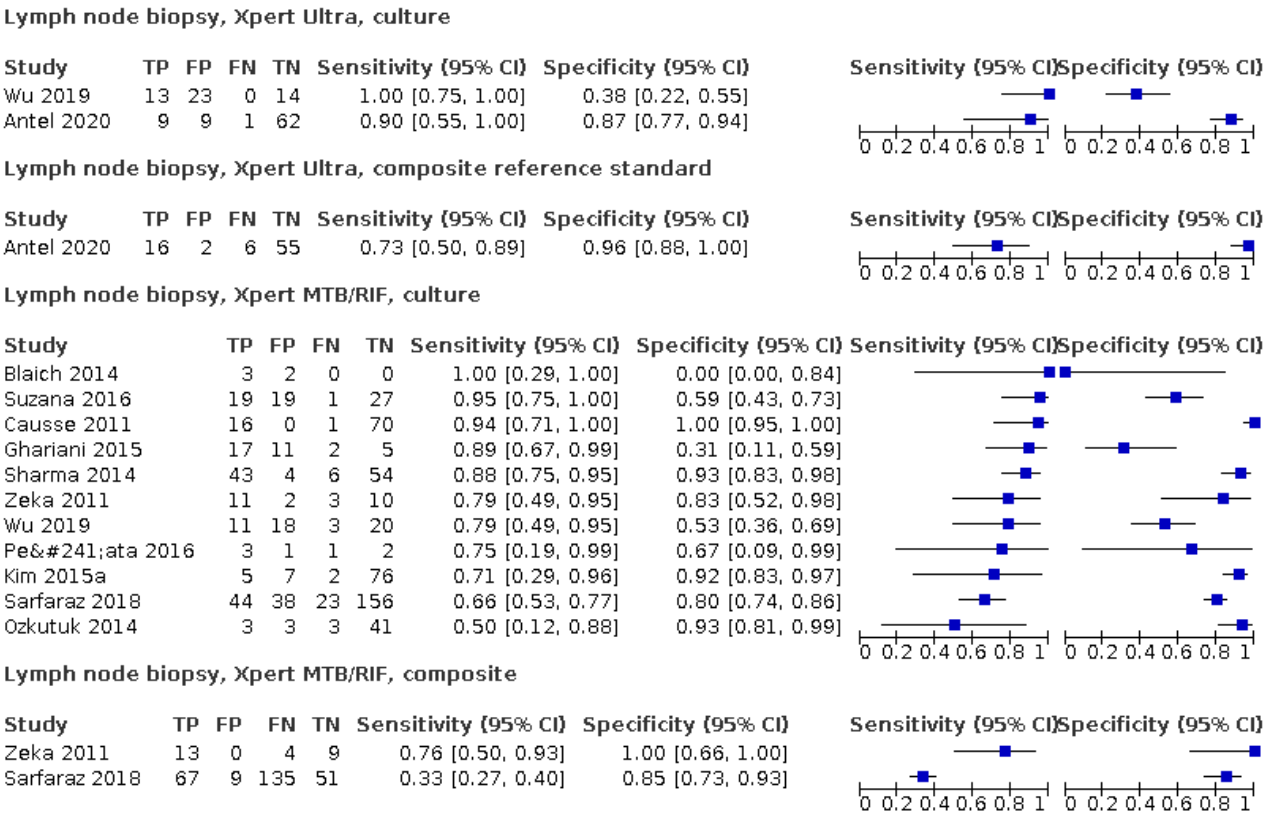
E: Xpert MTB/RIF and Xpert Ultra in lymph node biopsies for lymph node tuberculosis

Xpert Ultra

Culture reference standard

In lymph node biopsies, Xpert Ultra sensitivity and specificity against culture were 90% (55 to 100) and 87% (77 to 94) (Antel 2020) and 100% (75 to 100) and 38% (22 to 55) (Wu 2019), (2 studies; 131 participants, 23 (17.6%) with tuberculosis); Figure 14.

Figure 14. Forest plots of Xpert Ultra and Xpert MTB/RIFsensitivity and specificity in lymph node biopsy by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



Composite reference standard

In lymph node biopsies, Xpert Ultra sensitivity and specificity against a composite reference standard were 73% (50 to 89) and 96% (88 to 100) (Antel 2020), (1 study; 81 participants); Figure 14.

Xpert MTB/RIF

Culture reference standard

Eleven studies evaluated Xpert MTB/RIF in lymph node biopsies against culture (Blaich 2014; Causse 2011; Ghariani 2015; Kim 2015a; Ozkutuk 2014; Peñata 2016; Sarfaraz 2018; Sharma 2014; Suzana 2016; Wu 2019; Zeka 2011). Xpert MTB/RIF sensitivity ranged from 50% to 100% and specificity ranged from 0% to 100%; Figure 14. We could not explain the heterogeneity in accuracy estimates by study quality, small numbers, or other factors.

In lymph node biopsies, Xpert MTB/RIF pooled sensitivity and specificity against culture were 82.4% (73.5 to 89.7) and 80.3% (60.3 to 91.5), (11 studies; 786 participants, 220 (28.0%) with tuberculosis); Table 2.

Composite reference standard

In lymph node biopsies, Xpert MTB/RIF sensitivity and specificity against a composite reference standard were 33% (27 to 40) and 85% (73 to 93) (Sarfaraz 2018) and 76% (50 to 93) and specificity of 100% (66 to 100) (Zeka 2011) (2 studies; 288 participants); Figure 14.

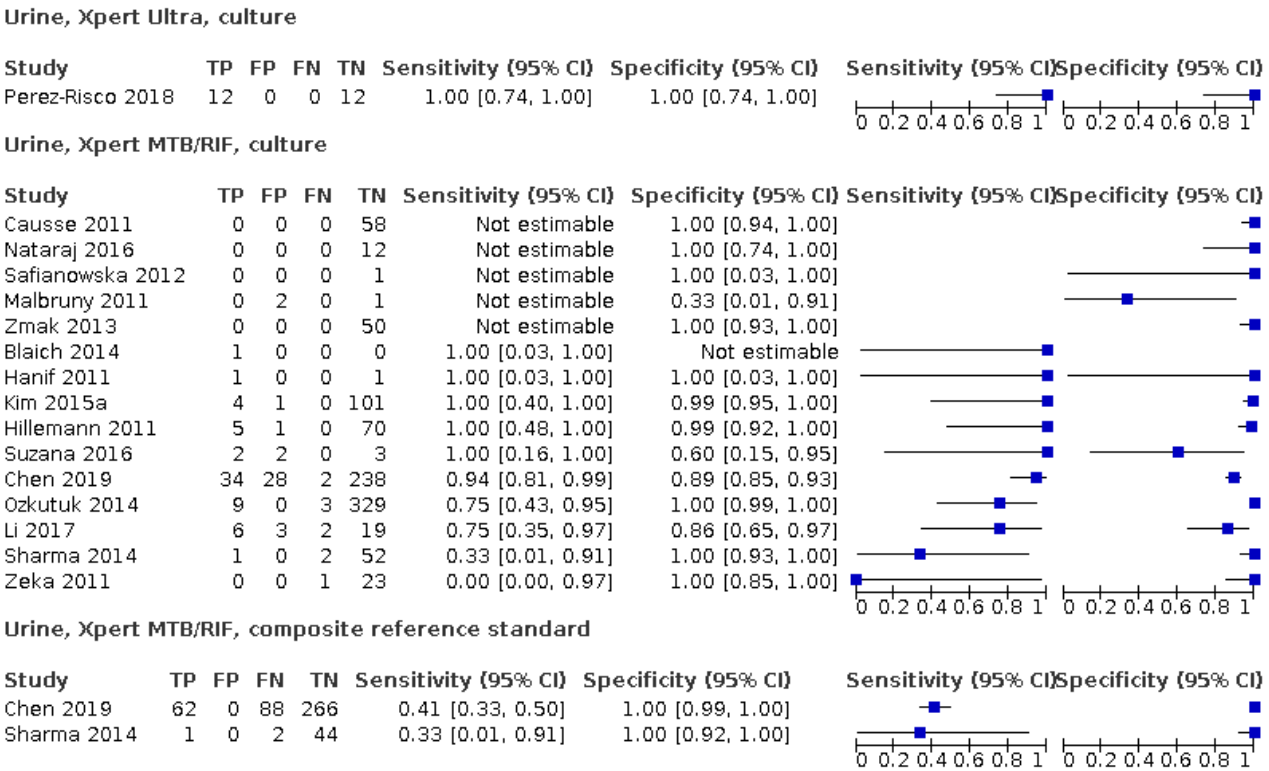
F: Xpert Ultra and Xpert MTB/RIF testing in urine for genitourinary tuberculosis

Xpert Ultra

Culture reference standard

In urine, Xpert Ultra sensitivity and specificity against culture were 100% (74 to 100) and 100% (74 to 100), (1 study; 24 participants, 12 (50%) with tuberculosis) (Perez-Risco 2018); Figure 15.

Figure 15. Forest plots of Xpert MTB/RIF and Xpert Ultra sensitivity and specificity in urine by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in urine against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Fifteen studies evaluated Xpert MTB/RIF in urine against culture (Blaich 2014; Causse 2011; Chen 2019; Hanif 2011; Hillemann 2011; Kim 2015a; Li 2017; Malbruny 2011; Nataraj 2016; Ozkutuk 2014; Safianowska 2012; Sharma 2014; Suzana 2016; Zeka 2011; Zmak 2013). Xpert MTB/RIF sensitivity ranged from 0% to 100% (sensitivity of 0% was reported by Zeka 2011 that had only one culture positive, which was Xpert negative) and specificity from 33% to 100% (Figure 15). Six studies (Blaich 2014; Causse 2011; Malbruny 2011; Nataraj 2016; Sharma 2014; Zmak 2013) did not contribute data to the meta-analysis because either sensitivity or specificity was not estimable.

In urine, Xpert MTB/RIF pooled sensitivity and specificity against culture were 85.9% (71.4 to 94.3) and 98.1% (93.1 to 99.7) (9 studies; 943 participants, 72 (7.6%) with tuberculosis); Table 2.

Composite reference standard

In urine, Xpert MTB/RIF sensitivity and specificity against a composite reference standard were 33% (1 to 91) and 100% (92 to 100) (Sharma 2014), and 41% (33 to 50) and 100% (99 to 100) (Chen 2019) (2 studies; 463 participants); Figure 15.

G: Xpert Ultra and Xpert MTB/RIF testing in bone or joint aspirate for bone or joint tuberculosis

Xpert Ultra

Culture reference standard

In bone or joint aspirate, Xpert Ultra sensitivity and specificity against culture were 88% (47 to 100) (specificity was not estimable) (Perez-Risco 2018), and 96% (87 to 100) and 97% (85 to 100) (Sun 2019) (2 studies; 94 participants, 60 (63.8%) with tuberculosis); Appendix 9.

Composite reference standard

In bone or joint aspirate, Xpert Ultra sensitivity and specificity against a composite reference standard were 96% (91 to 99) and 97% (85 to 100), (1 study; 145 participants; Sun 2019); Appendix 9.

Xpert MTB/RIF

Culture reference standard

Twelve studies evaluated Xpert MTB/RIF in bone or joint fluid for culture (Al-Ateah 2012; Blaich 2014; Gu 2015; Kim 2015a; Li 2017; Malbruny 2011; Nataraj 2016; Ozkutuk 2014; Peñata 2016; Safianowska 2012; Sun 2019; Suzana 2016). Xpert MTB/RIF

sensitivity ranged from 96% to 100% and specificity ranged from 53% to 100%; Appendix 9.

In bone or joint aspirate, Xpert MTB/RIF pooled sensitivity and specificity against culture were 97.9% (93.1 to 99.6) and 97.4% (80.2 to 100.0); (6 studies; 471 participants, 110 (23.4%) with tuberculosis); Table 2

Composite reference standard

In bone or joint aspirate, Xpert MTB/RIF sensitivity and specificity against a composite reference standard were 82% (69 to 91) and 100% (69 to 100) (Gu 2015), and 94% (87 to 97) and 100% (90 to 100) (Sun 2019); (2 studies; 205 participants); Appendix 9.

H: Xpert Ultra and Xpert MTB/RIF testing in tissue for bone or joint tuberculosis

Xpert Ultra

Culture reference standard

We did not identify any studies that evaluated Xpert Ultra in tissue for bone or joint tuberculosis against culture.

Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in tissue for bone or joint tuberculosis against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Three studies evaluated Xpert MTB/RIF in bone or joint tissue against culture. Xpert MTB/RIF sensitivity ranged from 50% to 100% and specificity ranged from 94% to 100% (Appendix 9).

In bone or joint tissue, Xpert MTB/RIF sensitivity and specificity (95% CI) against culture were 100% (3 to 100) and 100% (48 to 100) (Malbruny 2011), 100% (3 to 100) and 100% (40 to 100) (Ozkutuk 2014), and 50% (1 to 99) and 94% (71 to 100) (Peñata 2016); (3 studies; 30 participants, 4 (13.3%) with tuberculosis).

Composite reference standard

We did not identify any studies that evaluated Xpert MTB/RIF in tissue for bone or joint tuberculosis against a composite reference standard.

J: Xpert Ultra and Xpert MTB/RIF testing in peritoneal fluid for peritoneal tuberculosis

Xpert Ultra

Culture reference standard

In peritoneal fluid, Xpert Ultra sensitivity against culture was 33% (1 to 91) and specificity was not estimable (Perez-Risco 2018) (1 study; 3 participants); Appendix 10.

Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in peritoneal fluid against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Seventeen studies evaluated Xpert MTB/RIF in peritoneal fluid against culture (Al-Ateah 2012; Causse 2011; Iram 2015; Kim 2015a; Li 2017; Malbruny 2011; Ozkutuk 2014; Peñata 2016; Rufai 2017a; Safianowska 2012; Scott 2014; Sharma 2014; Suzana 2016; Ullah 2017; Vadwai 2011; Zeka 2011; Zmak 2013). Four studies (Al-Ateah 2012; Causse 2011; Iram 2015; Safianowska 2012) did not contribute data to the meta-analysis because sensitivity was not estimable. In individual studies, Xpert MTB/RIF sensitivity ranged from 33% to 100% and specificity ranged from 90% to 100%; Figure 16; Appendix 10.

Figure 16. Forest plots of Xpert MTB/RIF sensitivity and specificity for peritoneal TB (fluid and tissue) by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

Peritoneal fluid, Xpert Ultra, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perez-Risco 2018	1	0	2	0	0.33 [0.01, 0.91]	Not estimable

Peritoneal fluid, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Safianowska 2012	0	0	0	8	Not estimable	1.00 [0.63, 1.00]
Iram 2015	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Causse 2011	0	0	0	20	Not estimable	1.00 [0.83, 1.00]
Al-Ateah 2012	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Ullah 2017	4	4	0	48	1.00 [0.40, 1.00]	0.92 [0.81, 0.98]
Suzana 2016	2	2	0	12	1.00 [0.16, 1.00]	0.86 [0.57, 0.98]
Peñata 2016	1	0	0	14	1.00 [0.03, 1.00]	1.00 [0.77, 1.00]
Vadwai 2011	2	0	0	9	1.00 [0.16, 1.00]	1.00 [0.66, 1.00]
Malbruny 2011	1	0	0	2	1.00 [0.03, 1.00]	1.00 [0.16, 1.00]
Li 2017	3	2	1	48	0.75 [0.19, 0.99]	0.96 [0.86, 1.00]
Rufai 2017a	12	0	5	50	0.71 [0.44, 0.90]	1.00 [0.93, 1.00]
Scott 2014	19	3	13	104	0.59 [0.41, 0.76]	0.97 [0.92, 0.99]
Kim 2015a	4	0	5	50	0.44 [0.14, 0.79]	1.00 [0.93, 1.00]
Zmak 2013	1	0	2	7	0.33 [0.01, 0.91]	1.00 [0.59, 1.00]
Sharma 2014	3	1	13	85	0.19 [0.04, 0.46]	0.99 [0.94, 1.00]
Ozkutuk 2014	0	0	2	40	0.00 [0.00, 0.84]	1.00 [0.91, 1.00]
Zeka 2011	0	1	1	4	0.00 [0.00, 0.97]	0.80 [0.28, 0.99]

Peritoneal tissue, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bera 2015	2	2	2	22	0.50 [0.07, 0.93]	0.92 [0.73, 0.99]

Pericardial fluid, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Safianowska 2012	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Peñata 2016	0	0	0	2	Not estimable	1.00 [0.16, 1.00]
Kim 2015a	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Causse 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Ozkutuk 2014	0	0	0	18	Not estimable	1.00 [0.81, 1.00]
Vadwai 2011	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Zmak 2013	0	0	0	17	Not estimable	1.00 [0.80, 1.00]
Blaich 2014	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Ullah 2017	4	0	0	12	1.00 [0.40, 1.00]	1.00 [0.74, 1.00]
Zeka 2011	1	0	0	5	1.00 [0.03, 1.00]	1.00 [0.48, 1.00]
Pandie 2014	28	27	19	60	0.60 [0.44, 0.74]	0.69 [0.58, 0.78]
Sharma 2014	1	1	3	15	0.25 [0.01, 0.81]	0.94 [0.70, 1.00]
Suzana 2016	0	0	1	4	0.00 [0.00, 0.97]	1.00 [0.40, 1.00]

Pericardial fluid, Xpert MTB/RIF, composite reference standard

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pandie 2014	41	0	14	5	0.75 [0.61, 0.85]	1.00 [0.48, 1.00]
Sharma 2014	2	0	3	12	0.40 [0.05, 0.85]	1.00 [0.74, 1.00]

Blood, Xpert MTB/RIF, culture

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Zmak 2013	0	0	0	11	Not estimable	1.00 [0.72, 1.00]
Feasey 2013	5	4	4	61	0.56 [0.21, 0.86]	0.94 [0.85, 0.98]

In peritoneal fluid, Xpert MTB/RIF pooled sensitivity and specificity against culture were 59.1% (42.1 to 76.2) and 97.6% (95.4 to 98.9), (13 studies; 580 participants, 94 (16.2%) with tuberculosis); Table 2.

Composite reference standard

We did not identify any studies that evaluated Xpert MTB/RIF in peritoneal fluid against a composite reference standard.

K: Xpert Ultra and Xpert MTB/RIF testing in tissue for peritoneal tuberculosis

Xpert Ultra

Culture reference standard

We did not identify any studies that evaluated Xpert Ultra in peritoneal tissue against culture.

Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in peritoneal tissue against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

In peritoneal tissue, Xpert MTB/RIF sensitivity and specificity against culture were 50% (7 to 93) and 92% (73 to 99) (1 study; 28 participants; Bera 2015); Appendix 10.

Composite reference standard

We did not identify any studies that evaluated Xpert MTB/RIF in peritoneal tissue against a composite reference standard.

L: Xpert Ultra and Xpert MTB/RIF testing in pericardial fluid for pericardial tuberculosis

Xpert Ultra

Culture reference standard

We did not identify any studies that evaluated Xpert Ultra in pericardial fluid against culture.

Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in pericardial fluid against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Fourteen studies evaluated Xpert MTB/RIF in pericardial fluid against culture (Al-Ateah 2012; Blaich 2014; Causse 2011; Kim 2015a; Ozkutuk 2014; Pandie 2014; Peñata 2016; Safianowska 2012; Sharma 2014; Suzana 2016; Ullah 2017; Vadwai 2011; Zeka 2011; Zmak 2013). Xpert MTB/RIF sensitivity ranged from 0% to 100% and specificity ranged from 69% to 100% (Appendix 10). Nine studies (Al-Ateah 2012; Blaich 2014; Causse 2011; Kim 2015a; Ozkutuk 2014; Peñata 2016; Safianowska 2012; Vadwai 2011; Zmak 2013) did not contribute data to the meta-analysis because either sensitivity or specificity was not estimable.

In pericardial fluid, Xpert MTB/RIF pooled sensitivity and specificity against culture were 61.4% (32.4 to 82.4) and 89.7% (74.9 to 99.0), (5 studies; 181 participants, 57 (31.5%) with tuberculosis); Table 2; Appendix 10.

Composite reference standard

We did not identify any studies that evaluated Xpert MTB/RIF in pericardial fluid against a composite reference standard.

M: Xpert Ultra and Xpert MTB/RIF testing in blood for disseminated tuberculosis

Xpert Ultra

Culture reference standard

We did not identify any studies that evaluated Xpert Ultra in blood against culture.

Composite reference standard

We did not identify any studies that evaluated Xpert Ultra in blood against a composite reference standard.

Xpert MTB/RIF

Culture reference standard

Two studies evaluated Xpert MTB/RIF in blood against culture (Feasey 2013; Zmak 2013). However, only one of these studies reported tuberculosis culture-positives. Xpert MTB/RIF sensitivity and specificity against culture were 56% (21 to 86) and 94% (85 to 98) (1 study; 74 participants, 9 (12.2%) with tuberculosis (Feasey 2013)); Appendix 10.

Composite reference standard

We did not identify any studies that evaluated Xpert MTB/RIF in blood against a composite reference standard.

Nontuberculous mycobacteria

For Xpert Ultra, two studies provided data on a variety of NTMs that grew from the specimens tested to look for evidence of cross-reactivity. Donovan 2020 assessed Xpert Ultra specificity in CSF from more than 100 participants with nontuberculous meningitis and found zero positive Xpert Ultra results in those with a probable or possible diagnosis of tuberculous meningitis and in any participant with a confirmed diagnosis of nontuberculous meningitis. Perez-Risco 2018 assessed Xpert Ultra specificity using 20 culture-positive NTM specimens (covering a total of 18 species) and found that Xpert Ultra was negative for all specimens.

For Xpert MTB/RIF, we previously reported that in 10 studies involving 6975 specimens with 141 NTMs, Xpert MTB/RIF was negative in all specimens (Kohli 2018).

II. Detection of rifampicin resistance

Xpert Ultra and Xpert MTB/RIF testing for rifampicin resistance

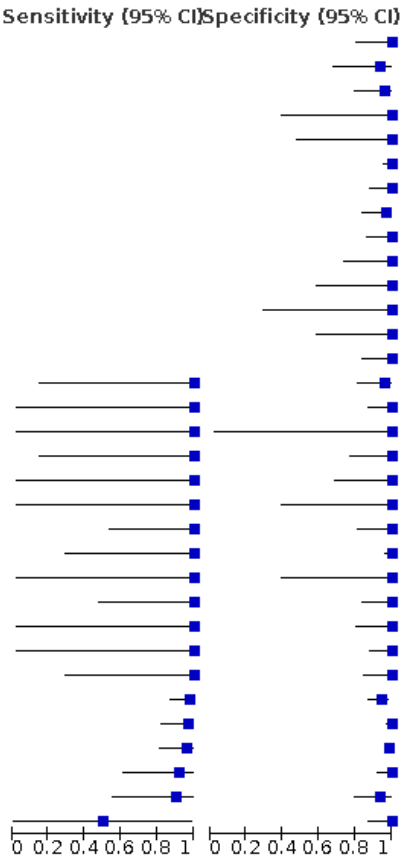
Xpert Ultra

Five studies evaluated Xpert Ultra for detection of rifampicin resistance. Xpert Ultra sensitivity estimates varied from 50% to 100%; specificity varied from 93% to 100%; Figure 17. One study reported zero participants with rifampicin resistance and thus sensitivity was not estimable (Chin 2019). Four studies contributed data to the bivariate meta-analysis (Sun 2019; Wang 2019; Wang 2020; Wu 2019). Xpert Ultra pooled sensitivity and specificity were 100.0% (95.1 to 100.0) and 100.0% (99.0 to 100.0), (4 studies; 129 participants, 24 (18.6%) with rifampicin resistance); Table 2.

Figure 17. Forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity for rifampicin resistance. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.

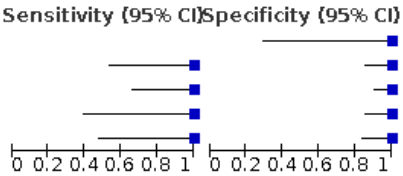
Rifampicin resistance, Xpert MTB/RIF

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blaich 2014	0	0	0	17	Not estimable	1.00 [0.80, 1.00]
Ablanedo-Terrazas 2014	0	1	0	14	Not estimable	0.93 [0.68, 1.00]
Hillemann 2011	0	1	0	24	Not estimable	0.96 [0.80, 1.00]
Iram 2015	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Feasey 2013	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Ghariani 2015	0	0	0	75	Not estimable	1.00 [0.95, 1.00]
Pandie 2014	0	0	0	28	Not estimable	1.00 [0.88, 1.00]
Ozkutuk 2014	0	1	0	31	Not estimable	0.97 [0.84, 1.00]
Lusiba 2014	0	0	0	25	Not estimable	1.00 [0.86, 1.00]
Malbruny 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Sharma 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Safianowska 2012	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Zmak 2013	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Zeka 2011	0	0	0	21	Not estimable	1.00 [0.84, 1.00]
Biadglegne 2014	2	1	0	26	1.00 [0.16, 1.00]	0.96 [0.81, 1.00]
Dhasmana 2014	1	0	0	26	1.00 [0.03, 1.00]	1.00 [0.87, 1.00]
Bera 2015	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Al-Ateah 2012	2	0	0	14	1.00 [0.16, 1.00]	1.00 [0.77, 1.00]
Hanif 2011	1	0	0	10	1.00 [0.03, 1.00]	1.00 [0.69, 1.00]
Friedrich 2011	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Gu 2015	6	0	0	18	1.00 [0.54, 1.00]	1.00 [0.81, 1.00]
Nhu 2014	3	0	0	104	1.00 [0.29, 1.00]	1.00 [0.97, 1.00]
Meldau 2014	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Wang 2020	5	0	0	21	1.00 [0.48, 1.00]	1.00 [0.84, 1.00]
Rufai 2015	1	0	0	17	1.00 [0.03, 1.00]	1.00 [0.80, 1.00]
Peñata 2016	1	0	0	28	1.00 [0.03, 1.00]	1.00 [0.88, 1.00]
Rufai 2017b	3	0	0	22	1.00 [0.29, 1.00]	1.00 [0.85, 1.00]
Vadwai 2011	39	5	1	80	0.97 [0.87, 1.00]	0.94 [0.87, 0.98]
Nataraj 2016	28	0	1	121	0.97 [0.82, 1.00]	1.00 [0.97, 1.00]
Sharma 2014	26	3	1	211	0.96 [0.81, 1.00]	0.99 [0.96, 1.00]
Li 2017	11	0	1	47	0.92 [0.62, 1.00]	1.00 [0.92, 1.00]
Du 2015	9	2	1	31	0.90 [0.55, 1.00]	0.94 [0.80, 0.99]
Ligthelm 2011	1	0	1	26	0.50 [0.01, 0.99]	1.00 [0.87, 1.00]



Rifampicin resistance, Xpert Ultra

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chin 2019	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Wang 2019	6	0	0	23	1.00 [0.54, 1.00]	1.00 [0.85, 1.00]
Sun 2019	9	0	0	38	1.00 [0.66, 1.00]	1.00 [0.91, 1.00]
Wu 2019	4	0	0	23	1.00 [0.40, 1.00]	1.00 [0.85, 1.00]
Wang 2020	5	0	0	21	1.00 [0.48, 1.00]	1.00 [0.84, 1.00]



Xpert MTB/RIF

Xpert MTB/RIF pooled sensitivity and specificity were 96.5% (91.9 to 98.8) and 99.1% (98.0 to 99.7) (19 studies; 970 participants, 148 (15.3%) with rifampicin resistance); Table 2; Figure 17.

Indeterminate Xpert Ultra and Xpert MTB/RIF results for rifampicin resistance

Xpert Ultra

Of the total 391 tests positive by Xpert Ultra, the proportion of indeterminate Xpert Ultra results for RIF resistance was 36.1%. All of these indeterminate results were Xpert Ultra trace-positive.

Xpert MTB/RIF

We previously reported that for rifampicin resistance testing, of 1003 tests performed, the pooled proportion of indeterminate Xpert MTB/RIF results was 2.6% (95% CrI 1.4 to 4.3) (Kohli 2018).

DISCUSSION

Summary of main results

This systematic review update summarizes the current literature and includes 69 unique studies on the accuracy of Xpert Ultra and Xpert MTB/RIF for extrapulmonary tuberculosis and rifampicin resistance. We identified 11 studies evaluating Xpert Ultra, an increase of 10 new studies since the original review (Kohli 2018). Unlike the original review, we limited inclusion to adults aged 15

years and older. We also include a composite reference standard in addition to a culture reference standard, and have stratified all analyses by type of reference standard. Major findings from our review include the following.

- Xpert Ultra sensitivity for tuberculosis varied across different types of specimens (from 75.0% in pleural fluid to 89.4% in cerebrospinal fluid); Table 2
- Xpert MTB/RIF sensitivity for tuberculosis varied across different types of specimens (from 49.5% in pleural fluid to 97.9% in bone or joint aspirate); Table 2
- Xpert MTB/RIF specificity in cerebrospinal fluid, pleural fluid, urine, bone or joint aspirate, and peritoneal fluid was ≥ 96.9%, against culture; overall, Xpert Ultra specificities were lower than those of Xpert MTB/RIF against culture, but against a composite reference standard results for both index tests were similar; Table 2
- In cerebrospinal fluid, Xpert Ultra sensitivity and specificity were 89.4% (79.1 to 95.6) and 91.2% (83.2 to 95.7) against culture; Summary of findings 1.
- In cerebrospinal fluid, Xpert MTB/RIF sensitivity and specificity were 71.1% (62.8 to 79.1) and 96.9% (95.4 to 98.0) against culture; Summary of findings 1
- In pleural fluid, Xpert Ultra sensitivity and specificity were 75.0% (58.0 to 86.4) and 87.0% (63.1 to 97.9) against culture; Summary of findings 2
- In pleural fluid, Xpert MTB/RIF sensitivity and specificity were 49.5% (39.8 to 59.9) and 98.9% (97.6 to 99.7) against culture; Summary of findings 2
- In lymph node aspirate, Xpert Ultra sensitivity and specificity were 70% (51 to 85) and 100% (92 to 100) against a composite reference standard (1 study); Summary of findings 3
- In lymph node aspirate, Xpert MTB/RIF sensitivity and specificity were 81.6% (61.9 to 93.3) and 96.4% (91.3 to 98.6) against a composite reference standard; Summary of findings 3
- For rifampicin resistance, Xpert Ultra sensitivity and specificity were 100.0% (95.1 to 100.0) and 100.0% (99.0 to 100.0); Summary of findings 4
- For rifampicin resistance, Xpert MTB/RIF sensitivity and specificity were 96.5% (91.9 to 98.8) and 99.1% (98.0 to 99.7); Summary of findings 4

Xpert Ultra and Xpert MTB/RIF testing in cerebrospinal fluid

(Summary of findings 1)

Xpert Ultra

Results of these studies indicate that in theory, for a population of 1000 people where 100 have tuberculosis meningitis on culture, 168 would be Xpert Ultra-positive: of these, 79 (47%) would not have tuberculosis (false-positives); and 832 would be Xpert Ultra-negative: of these, 11 (1%) would have tuberculosis (false-negatives).

Xpert MTB/RIF

Results of these studies indicate that in theory, for a population of 1000 people where 100 have tuberculosis meningitis on culture, 99 would be Xpert MTB/RIF-positive: of these, 28 (28%) would not have tuberculosis (false-positives); and 901 would be Xpert MTB/RIF-negative: of these, 29 (3%) would have tuberculosis (false-negatives).

Rapid diagnosis of tuberculous meningitis is critical so that lifesaving treatment can be started promptly. Around 50% of those affected die or experience disabling consequences (Thwaites 2013). Xpert Ultra was designed to improve tuberculosis detection, in particular in people with paucibacillary disease. The limit of detection for MTB is lower with Xpert Ultra (16 bacterial colony-forming units (cfu) per mL) than with Xpert MTB/RIF (131 cfu per mL) (Chakravorty 2017). In studies that compared Xpert Ultra and Xpert MTB/RIF in the same participants, we found Xpert Ultra to have higher pooled sensitivity (89.0%) than Xpert MTB/RIF (62.2%), and lower pooled specificity (91.0%) than Xpert MTB/RIF (96.8%) for tuberculous meningitis. In addition, in subgroup analyses we found slightly higher Xpert Ultra accuracy in studies that concentrated the cerebrospinal fluid (CSF): pooled sensitivity of 90.5% in concentrated specimens versus 88.4% in unconcentrated specimens; and pooled specificity of 91.9% in concentrated specimens versus 88.6% in unconcentrated specimens. We note that subgroup findings should be interpreted with caution, as there were only three studies and a small number of tuberculous meningitis cases included. The Tuberculous Meningitis International Research Consortium has recommended increasing the volume of CSF collected for diagnosis followed by centrifugation as a way of improving Xpert MTB/RIF assay sensitivity (Bahr 2016); however, we did not have sufficient data to investigate CSF collection volume. Increased Xpert MTB/RIF sensitivity in HIV-positive people compared with HIV-negative people has been reported, with the increased bacterial burden in tuberculosis and HIV co-infection proposed as the reason (Patel 2013). We had limited data to investigate this for Xpert Ultra as we identified only two studies in HIV-positive people, with sensitivities of 90% (Bahr 2017) and 89% (Cresswell 2020).

Xpert Ultra and Xpert MTB/RIF testing in pleural fluid

(Summary of findings 2)

Xpert Ultra

Results of these studies indicate that in theory, for a population of 1000 people where 100 have pleural tuberculosis on culture, 192 would be Xpert Ultra-positive: of these, 117 (61%) would not have tuberculosis (false-positives); and 808 would be Xpert Ultra-negative: of these, 25 (3%) would have tuberculosis (false-negatives).

Xpert MTB/RIF

Results of these studies indicate that in theory, for a population of 1000 people where 100 have pleural tuberculosis on culture, 60 would be Xpert MTB/RIF-positive: of these, 10 (17%) would not have tuberculosis (false-positives); and 940 would be Xpert MTB/RIF-negative: of these, 50 (5%) would have tuberculosis (false-negatives).

With the bivariate model, we found Xpert Ultra to have higher pooled sensitivity (75.0%) than Xpert MTB/RIF (49.6%) and lower pooled specificity (87.0%) than Xpert MTB/RIF (98.7%) in pleural fluid against a culture reference standard, between-study comparison. Based on the latent class meta-analysis model, Xpert Ultra pooled sensitivity was comparable (76.0%) and specificity higher (99.5%) than what was obtained when culture was treated

as having perfect accuracy. Xpert Ultra pooled sensitivity in pleural fluid was lower than that of CSF. One reason for the lower sensitivity of Xpert Ultra in pleural fluid could be the paucibacillary nature of pleural tuberculosis. Other possible reasons are contamination of blood or the presence of certain polymerase chain reaction (PCR) inhibitors in the pleural fluid (Pai 2004; Woods 2001). However, Theron and colleagues found that extrapulmonary specimens showed less evidence of PCR inhibition than pulmonary specimens, with bacterial load being more important for a positive Xpert MTB/RIF result (Theron 2014b). Given that false-negative results were common (low sensitivity), a negative Xpert Ultra or Xpert MTB/RIF result may not be relied on to exclude tuberculosis.

Xpert Ultra testing in lymph node aspirates

Xpert Ultra

Results of these studies indicate that in theory, for a population of 1000 people where 100 have lymph node tuberculosis verified by a composite reference standard, 70 would be Xpert Ultra-positive: of these, 0 (0%) would not have tuberculosis (false-positives); and 930 would be Xpert Ultra-negative: of these, 30 (3%) would have tuberculosis (false-negatives).

Xpert MTB/RIF

Results of these studies indicate that in theory, for a population of 1000 people where 100 have lymph node tuberculosis verified by a composite reference standard, 118 would be Xpert MTB/RIF-positive: of these 37 (31%) would not have tuberculosis (false-positives); and 882 would be Xpert MTB/RIF-negative: of these 19 (2%) would have tuberculosis (false-negatives).

Regarding Xpert testing for lymph node aspirate, it important to point out that although tissue biopsy provides material for histological examination which may be of substantial diagnostic value, a fluid specimen may be collected more easily. In addition, fine-needle aspiration of lymph nodes is well suited for use in resource-limited settings because the procedure is simple, easy to learn, minimally invasive, and inexpensive (Wright 2009b). Thus clinicians may want to consider fine-needle aspiration of lymph nodes before surgical biopsy.

In our review, using a standard bivariate meta-analysis model, Xpert MTB/RIF pooled specificity (defined by culture) in lymph node aspirate was 86.0%, whereas with a composite reference standard pooled specificity increased to 95.9%. Using a latent class meta-analysis model with informative priors, Xpert MTB/RIF pooled specificity increased to 99.5%. In previous meta-analyses, Xpert MTB/RIF specificity for lymph node tuberculosis (aspirate and tissue) against culture as a reference standard was 94% (Denkinger 2014), 93% (Maynard-Smith 2014), and 92% (Penz 2015). See Table 8. Using a composite reference standard (defined by the primary study authors), Denkinger 2014 found increased Xpert MTB/RIF specificity of 99% for lymph node tuberculosis (5 studies, 728 specimens). Thus, it appears that accuracy results depend in part on the choice of reference standard. Regarding the use of a composite reference standard, owing to differing definitions and difficulty in interpreting them, there is a risk of bias (Schiller 2016) (see section Strengths and weaknesses of the review).

We considered several reasons why the specificity of Xpert Ultra (78%) and Xpert MTB/RIF (86.0%) in lymph node aspirate against culture would be lower than in other extrapulmonary specimens. Although not always reported, studies may have included participants receiving tuberculosis treatment. We previously reported that in a sensitivity analysis limiting inclusion to studies that involved participants not receiving tuberculosis treatment, specificity increased from 86% to 89% (Kohli 2018). We considered the type of culture used in the included studies because liquid culture is more sensitive than solid culture (American Thoracic Society 2000). Most studies used liquid culture or a combination of solid and liquid culture. The single study evaluating Xpert Ultra used liquid culture. Only two of the 15 studies (13%) evaluating Xpert MTB/RIF exclusively used solid culture. Culture results may also be negative owing to inefficient specimen collection or errors in sampling, differing bacterial load, and contamination (Wright 2009b). Negative culture results in lymph node tuberculosis have previously been reported (Fontanilla 2011).

Another reason for negative culture results is that there may have been a decrease in live tuberculosis bacteria during processing with N-acetyl-L-cysteine-sodium hydroxide, which is routinely used to homogenize, decontaminate, and liquefy non-sterile specimens, such as sputum, for mycobacterial culture (American Thoracic Society 2000). Harsh decontamination practices have been noted to contribute to false-negative culture results, especially in paucibacillary specimens (FIND 2017). Standards specify, "specimens collected from normally sterile sites may be placed directly into the culture medium" (American Thoracic Society 2000). CSF, pleural fluid, and lymph node aspirates are usually considered to be sterile specimens. It is our understanding that some laboratories do decontaminate sterile site specimens as a precaution against non-sterile collection procedures. In this review, 47% of the studies reported decontaminating lymph node aspirates before culture inoculation. We did not have sufficient data to further investigate laboratory practices.

In summary, several factors probably contributed to low Xpert MTB/RIF specificity against culture in lymph node aspirate. The 'true' specificity of Xpert MTB/RIF in lymph node aspirate is likely to be higher owing to the aforementioned reasons. Xpert MTB/RIF specificity was higher against a composite reference standard and with application of latent class analysis, similar to that found in CSF, pleural fluid, and other specimens (Table 2; Table 3).

We investigated the prevalence of extrapulmonary tuberculosis (confirmed by culture) as a potential source of heterogeneity because changes in disease prevalence have often been found to be associated with other important changes, such as changes in the disease spectrum, which may affect diagnostic accuracy estimates (Leeflang 2013). For Xpert MTB/RIF, for pleural fluid and lymph node aspirate, we found that pooled sensitivity was higher in settings with higher tuberculosis prevalence. In all analyses, for both Xpert Ultra (CSF) and Xpert MTB/RIF (CSF, pleural fluid, and lymph node aspirate), specificity in settings with higher tuberculosis prevalence was similar or lower than in settings with lower tuberculosis prevalence. Findings from additional analyses are available in the previous version of this review (Kohli 2018).

Xpert Ultra and Xpert MTB/RIF testing for rifampicin resistance

(Summary of findings 4)

Xpert Ultra

Results of these studies indicate that in theory, for a population of 1000 people where 100 have rifampicin resistance, 100 would

be Xpert Ultra-positive (resistant): of these, zero (0%) would not have rifampicin resistance (false-positives); and 900 would be Xpert Ultra-negative (susceptible): of these, zero (0%) would have rifampicin resistance.

Xpert MTB/RIF

Results of these studies indicate that in theory, for a population of 1000 people where 100 have rifampicin resistance, 105 would be Xpert MTB/RIF-positive (resistant): of these, 8 (8%) would not have rifampicin resistance; and 895 would be Xpert MTB/RIF-negative (susceptible): of these, 3 (0.3%) would have rifampicin resistance.

For detection of rifampicin resistance in extrapulmonary specimens, we found the sensitivity of Xpert Ultra (100%) and Xpert MTB/RIF (96.7%) and the specificity of Xpert Ultra (100%) and Xpert MTB/RIF (99.1%), to be comparable to estimates in pulmonary specimens: sensitivity (96%) and specificity (98%) (Horne 2019). We caution that the results for Xpert Ultra are based on only four studies, involving 129 participants, 24 (18.6%) with rifampicin resistance. Nonetheless, these findings suggest that the use of Xpert Ultra and Xpert MTB/RIF in extrapulmonary specimens could assist in rapid diagnosis of rifampicin-resistant tuberculosis and early initiation of treatment for multidrug-resistant tuberculosis (MDR-TB).

Notably, concerns have been raised about rapid drug susceptibility testing (DST) methods, in particular automated mycobacteria growth indicator tube (MGIT) 960 for tuberculosis drug resistance using the recommended critical concentrations. As a priority, the WHO is planning to re-evaluate the critical concentrations for rifampicin (WHO 2018).

For Xpert Ultra, we found a high rate (36.1%) of indeterminate rifampicin resistance results, all owing to trace call results. This finding was expected since, for trace call results, rifampicin resistance cannot be determined. Xpert Ultra incorporates two new multi-copy amplification targets (IS*6110* and IS*1081*). Trace call indicates that only the multi-copy targets were detected, and not the tuberculosis-specific regions in the *rpoB* gene. Resistance to rifampicin has mainly been associated mainly with mutations in a limited region of the *rpoB* gene (Telenti 1993).

People-important outcomes, such as mortality, are especially relevant to patients, decision-makers, and the wider tuberculosis community. While performing this systematic review, we did not identify direct evidence of studies linking true-positives, false-positives, true-negatives, and false-negatives to people-important outcomes when either Xpert Ultra or Xpert MTB/RIF was used to diagnose extrapulmonary tuberculosis. To our knowledge, for pulmonary tuberculosis, there have been two systematic reviews of randomized trials on the impact of the use of Xpert MTB/RIF on health outcomes. Both reviews compared the effect of Xpert MTB/RIF and smear microscopy on all-cause mortality; Di Tanna and colleagues summarized the accuracy of Xpert MTB/RIF in an individual patient-level data meta-analysis (3 trials, 8143 participants) (Di Tanna 2019) and Haraka and colleagues performed a random-effects meta-analysis, (5 trials, 10,409 participants (Haraka 2018; WHO Consolidated Guidelines (Module 3) 2020). In both reviews, Xpert MTB/RIF did not show a statistically significant effect on all-cause mortality, although the direction of effect was towards mortality reduction. Insufficient power to detect mortality in randomized trials measuring the impact of diagnostic tests on patient-important outcomes has been discussed previously as a limitation of such trials (Di Tanna 2019; Schumacher 2019). Larger sample sizes are needed to evaluate the effect of Xpert MTB/RIF on mortality, but achieving this is difficult in pragmatic situations. For example, Schumacher 2019 showed that a sample size of 31,000 participants would be needed if researchers were to plan a cluster-randomized diagnostic trial using the baseline mortality and effect size demonstrated by the individual patient data from Di Tanna 2019.

This review represents the most comprehensive review of the diagnostic accuracy of Xpert Ultra and Xpert MTB/RIF for extrapulmonary tuberculosis in adults. For Xpert MTB/RIF, our previous review (Kohli 2018) provides additional findings. These reviews provide evidence that may help countries to make decisions about scaling up the tests for programmatic management of tuberculosis and drug-resistant tuberculosis. Although the information in this review will help to inform such decisions, other factors such as resource requirements and feasibility (including stable electrical power supply, temperature control, and maintenance of the cartridge modules) will also be important considerations.

Strengths and weaknesses of the review

Completeness of evidence

This is a reasonably complete data set. We included any non-English studies that we found from which we could obtain accuracy data. However, we acknowledge that we may have missed some studies despite the comprehensive search and our outreach to investigators. We included eight common forms of extrapulmonary tuberculosis in the review. However, for some of these forms, such as disseminated tuberculosis, data were insufficient to allow us to determine summary accuracy estimates. We did not include less common forms, such as cutaneous tuberculosis, ocular tuberculosis, female genital tuberculosis, and tuberculosis of the breast. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy (PRISMA-DTA) (McInnes 2018).

Accuracy of the reference standards used

In a systematic review of diagnostic test accuracy studies, the reference standard is the best available test to determine the presence or absence of the target condition. In this review, we used two reference standards: culture and a composite reference standard, both of which are known to be imperfect. While the composite reference standard is designed to have improved accuracy compared to culture alone, it may still lead to biased accuracy estimates of the index test, depending on various factors such as the accuracy of the different components; decision rules for combining them; prevalence of the target condition; and conditional dependence between the components and the index test (Schiller 2016). Conditional dependence between two imperfect tests arises when both tests make the same false-positive or false-negative errors more often than expected by chance (Naaktgeboren 2013). Hence, conditional dependence may arise between the index test and both reference standards we have used, as they are imperfect. As a consequence, we may over- or underestimate the diagnostic accuracy of the index tests. An additional challenge with including a composite reference standard is that the definition of the composite reference standard may vary across studies, making it difficult to interpret the accuracy

estimates. To adjust for the imperfect accuracy of culture, we applied a latent class model when evaluating Xpert MTB/RIF sensitivity and specificity, for which there were a larger number of studies. We added parameters for the sensitivity and specificity of culture and terms for conditional dependence to adjust for the dependence between Xpert MTB/RIF and culture among disease-positive and disease-negative participants. In this way, we were able to improve estimation of both the pooled sensitivity and specificity of Xpert MTB/RIF, as well as between-study variability. An adequate number of studies is needed for a sufficiently robust model to estimate these additional parameters. We therefore found that we were unable to do the same for meta-analyses of the accuracy for Xpert Ultra owing to the small number of studies, many of which had small sample sizes resulting in zero cell counts.

Several factors may have contributed to false-negative culture results for the accuracy of the reference standard for lymph node aspirate in particular, including inefficient specimen collection and overly harsh decontamination. For this particular analysis, we were able to take advantage of the Bayesian estimation approach to incorporate prior information on Xpert MTB/RIF and culture specificity. This allowed us to make the best use of data from the included studies and our knowledge of the performance of Xpert MTB/RIF. We had insufficient data to apply the latent class model to data from the single study evaluating Xpert Ultra in lymph node aspirates.

Establishing a diagnosis of extrapulmonary tuberculosis would ideally include pursuing the diagnosis of pulmonary tuberculosis as well, because participants with tuberculosis may have both pulmonary and extrapulmonary tuberculosis and the lung may be the only site where the presence of tuberculosis can be established. Because of the difficulties involved in diagnosing HIV-associated tuberculosis, it is recommended that multiple cultures from sputum and other types of specimens be evaluated in people living with HIV (Bjerrum 2019; Shah 2016b). Given the limitations in the reference standard, we recommend that future studies consider using liquid culture because this is more sensitive than solid culture, and that researchers obtain multiple specimens for culture to confirm the diagnosis of extrapulmonary tuberculosis (Drain 2019).

Most studies included in this review used culture-based DST (either Löwenstein-Jensen (LJ) or mycobacteria growth indicator tube (MGIT) 960) as the reference standard for detection of rifampicin resistance. Concerns have been raised about rapid DST methods, in particular automated MGIT 960, for tuberculosis drug resistance using the recommended critical concentrations. The WHO is planning to prioritise a re-evaluation of the critical concentrations for rifampicin (WHO 2018).

We assessed the number of specimens with nontuberculous mycobacteria (NTMs) that were Xpert Ultra-positive. In two studies that reported 120 NTMs, Xpert Ultra was negative in all specimens. In the previous version of this review, among 10 studies that reported information comprising 141 NTMs, Xpert MTB/RIF was negative in all specimens (Kohli 2018).

Quality and quality of reporting of the included studies

Risk of bias was low for the participant selection, index test, and flow and timing domains and was high or unclear for the reference standard domain (most of these studies performed specimen decontamination before culture inoculation). A limitation was that several studies included more than one specimen per participant, which artificially inflated the sample size of the study and may have led to overestimation or underestimation of the accuracy estimates. In general, studies were fairly well reported, although we corresponded with almost all primary study authors to ask for additional data and missing information. In several studies, accuracy data by site of extrapulmonary disease were not reported, and in a minority of studies, blinding was not reported. We strongly encourage the authors of future studies to follow the recommendations provided in the updated Standards for Reporting Diagnostic Accuracy (STARD) statement to improve the quality of reporting (Bossuyt 2015).

Interpretability of subgroup analyses

We investigated potential sources of heterogeneity in the different extrapulmonary specimens. Importantly, we found slightly higher Xpert Ultra accuracy in studies with concentrated cerebrospinal fluid (CSF) in comparison to unconcentrated specimens. We note that subgroup findings should be interpreted with caution, as there were only three studies and a small number of tuberculous meningitis cases included in these analyses.

Comparison with other systematic reviews

We are aware of several systematic reviews previously published on this topic that estimated summary accuracy of Xpert MTB/RIF for distinct forms of extrapulmonary tuberculosis, as well as different forms of extrapulmonary tuberculosis combined (Table 8). We identified one systematic review that estimated summary accuracy of Xpert Ultra that found, for all forms of extrapulmonary tuberculosis combined, pooled sensitivity and specificity of 85.1% (95% CI 76.7 to 90.8%) and 95.7% (95% CI 87.9 to 98.6%), (7 studies; 1500 specimens) (Zhang 2020).

Compared with previous systematic reviews, our review extends the date of the search for potential studies for inclusion. Our strict inclusion criteria, e.g. excluding case-control studies, meant that some of the studies included in other reviews were excluded from ours.

Applicability of findings to the review question

For the participant selection domain, most studies had high or unclear concern for applicability because either participants were evaluated exclusively as inpatients in tertiary care or we were not sure about the clinical settings. We therefore cannot be sure about the applicability of our findings to primary care. Studies that take place in referral settings may include participants whose condition is more difficult to diagnose than are seen at lower levels of the health system. However, we recognize that classifying studies as primary, secondary, or tertiary care may not adequately account for differences in disease spectrum (Leeflang 2013). For the index and reference test domains, most studies had low concern for applicability.

AUTHORS' CONCLUSIONS

Implications for practice

In people presumed to have extrapulmonary tuberculosis, Xpert Ultra and Xpert MTB/RIF may be helpful in confirming the diagnosis. Sensitivity varies across different extrapulmonary specimens, while for most specimens specificity is high, the test rarely yielding a

positive result for people without tuberculosis. For tuberculous meningitis, Xpert Ultra had higher pooled sensitivity and lower pooled specificity than Xpert MTB/RIF against culture. Xpert Ultra and Xpert MTB/RIF had similar sensitivity and specificity for rifampicin resistance.

Implications for research

Future studies should perform comparisons of different tests, including Xpert Ultra, as this approach will reveal which tests (or strategies) yield superior diagnostic accuracy. For these studies, the preferred study design is one in which all participants receive all available diagnostic tests or are randomly assigned to receive one or another of the tests. Studies should include children and people living with HIV. Future research should acknowledge the concern associated with culture as a reference standard in paucibacillary specimens, and should consider ways to address this limitation.

Rapid point-of-care diagnostic tests for extrapulmonary tuberculosis are critically needed. Research groups should focus on developing diagnostic tests and strategies that use readily-available clinical specimens, such as urine, rather than specimens that require invasive procedures for collection.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ablanedo-Terrazas 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: HIV-positive patients with palpable cervical lymph nodes Age: median 29 years [interquartile range (IQR) 24 to 36] Sex, female: 12% Children: no HIV infection: 100% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 15 Laboratory level: central Country: Mexico World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO standard operating procedure (SOP) or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node (LN) TB Reference standard for TB detection: Löwenstein–Jensen (LJ) and Mycobacterium growth indicator tube (MGIT) Reference standard for rifampicin resistance: not reported Speciation: yes Decontamination: yes, N-acetyl-L-cysteine-sodium hydroxide (NALC-NaOH)
Flow and timing	

Ablanedo-Terrazas 2014 *(Continued)*

Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Ablanedo-Terrazas 2014 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Ajbani 2018

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: neck rigidity, vomiting, fever, headache and seizures Age: 13 and older Sex, female: 46% Children: no HIV infection: not reported Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 13 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: not reported Decontamination: no
Target condition and reference standard(s)	TB meningitis MGIT Speciation: yes
Flow and timing	
Comparative	

Ajbani 2018 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Ajbani 2018 *(Continued)*

Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Al-Ateah 2012

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients suspected of having extrapulmonary TB Age: median 35 years Sex, female: 45% Children: 3% HIV infection: 0% Clinical setting: tertiary care centre (laboratory-based evaluation) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 67 Laboratory level: central Country: Saudi Arabia World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB, pleural TB Reference standards for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-drug susceptibility testing (DST) Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	

Al-Ateah 2012 *(Continued)*

Comparative			
Notes	Site of extrapulmonary disease was not reported for 16 tissue specimens and 10 abscesses		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Al-Ateah 2012 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Antel 2020

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: suspected tuberculosis adenitis Age: ≥ 18 years; median 37 years (IQR 30 to 49) Sex, female: 55% Children: no HIV infection: 51% Clinical setting: tertiary referral centre, inpatients and outpatients, most participants (84%) were seen as outpatients, high percentage received prior testing for tuberculosis, see note Past history of TB: 24% Patients on anti-TB treatment: 21% Number of specimens evaluated: 99 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert Ultra
Target condition and reference standard(s)	Target condition: lymph node tuberculosis, specimen collected by fine-needle biopsy and core-needle biopsy Reference standard: MGIT Target condition: rifampicin resistance Reference standard: MTBDR*plus* Speciation: yes, MTBDR*plus*

Antel 2020 *(Continued)*

	Decontamination: no
Flow and timing	
Comparative	
Notes	"A high proportion of participants had tuberculosis investigations prior to referral and the frequency of positive results were: sputum Xpert 3/22, urinary LAM 1/5, and tuberculosis culture (5/15) (by site: urine 0/1, blood 1/2, sputum 4/12, lymph node 0/1 (tissue)). Chest x-ray had been performed in 36% and reported as 'suggestive of tuberculosis' by the referring clinician in 28% of these."

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Antel 2020 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Azevedo 2018

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, retrospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected meningitis Age: > 16 years Sex, female: not reported Children: no HIV infection: 100% Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 101 Laboratory level: central, university medical centre Country: Brazil

Azevedo 2018 *(Continued)*

	World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: no		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: not reported		
Target condition and reference standard(s)	TB meningitis Culture not otherwise specified; CRS: uniform case definition Speciation: not reported Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear

Azevedo 2018 *(Continued)*

DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bahr 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected patients presenting with symptoms of meningitis being evaluated for cryptococcal meningitis. All persons who were CSF cryptococcal antigen-negative had a TB workup Age: median 40 years (IQR 30 to 45) Sex, female: 34% Children: no HIV infection: 98% Clinical setting: tertiary care centre (Inpatient) Past history of TB: 22% Participants on anti-TB treatment: yes, 11% Number of specimens evaluated: 80 Laboratory level: central

Bahr 2015 *(Continued)*

	Country: Uganda World Bank Income Classification: low income High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: TB meningitis Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes	Reference standards were culture and a TB meningitis uniform case definition		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Bahr 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bahr 2017

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected patients presenting with symptoms of meningitis being evaluated for cryptococcal meningitis. All persons who were CSF cryptococcal antigen-negative had a TB workup Age: TB meningitis: median 32 years (IQR 30 to 34); other meningitis: 34 years (IQR 29 to 43) Sex, female: 45% Children: no HIV infection: 100% Clinical setting: tertiary care centre (inpatient) Past history of TB: 6%

Bahr 2017 *(Continued)*

	Participants on anti-TB treatment: yes, 2% Number of specimens evaluated: 129 Laboratory level: central Country: Uganda World Bank Income Classification: low income High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: TB meningitis Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	This study evaluated Xpert MTB/RIF and Xpert MTB/RIF Ultra. Reference standards were culture and a TB meningitis uniform case definition

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern

Bahr 2017 *(Continued)*

DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Bera 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with exudative ascites (lymphocytic ascites and ascitic fluid protein content > 2.5 g/dL) Age: mean 43 years (standard deviation (SD) 15 years) Sex, female: 29% Children: no HIV infection: not reported Clinical setting: tertiary care centre (outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 28 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: not reported Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: peritoneal TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: LJ and MGIT-DST Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	"The study included only smear-negative specimens, however, the study excluded specimens that were negative for malignant cells on prior testing (i.e. cytology)"
Methodological quality	

Bera 2015 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Bera 2015 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Biadglegne 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with enlarged lymph nodes not responding to a 2-week course of antibiotics and clinically suspected for TB lymphadenitis Age: ≤ 14 years: 15%; > 14 years: 85% Sex, female: 57% Children: 15% HIV infection: not reported Clinical setting: tertiary care centres (multicentre study) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 213 Laboratory level: intermediate Country: Ethiopia World Bank Income Classification: low income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard for TB detection: LJ and Gottsascker and BacT/ALERT 3D Reference standard for rifampicin resistance: MTBDR*plus* and BacT-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	

Biadglegne 2014 *(Continued)*

Notes	Total number of participants: 231; included: 213 (excluded: contaminated = 11; invalid/error = 7)		

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		

Biadglegne 2014 *(Continued)*

Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Blaich 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspicion of extrapulmonary TB Age: median 34 (IQR 30 to 52) Sex, female: 46% Children: no HIV infection: yes, 8% Clinical setting: university hospital (inpatient and outpatient) Past history of TB: yes, 11% Patients on anti-TB treatment: no Number of specimens evaluated: 20 Laboratory level: central Country: Switzerland World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for lymph node aspirate, bone and joint fluid, urine, peritoneal fluid, and lymph node tissue; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, lymph node TB, pericardial TB, genitourinary TB, bone and joint TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes

Blaich 2014 *(Continued)*

	Decontamination: yes, NALC-NaOH for all specimens except pleural fluid and CSF		
Flow and timing			
Comparative			
Notes	Study included 1 bone marrow specimen that consisted of both aspirate and tissue		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	

Blaich 2014 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Causse 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: median 45 years, range 5 to 83 years Sex, female: 31% Children: yes, 15% HIV infection: not reported Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 261 Laboratory level: central Country: Spain World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, peritoneal TB, pericardial TB, genitourinary TB

Causse 2011 *(Continued)*

	Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: not reported Speciation: yes Decontamination: yes, NALC-NaOH for all specimens except pleural fluid and CSF
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		

Causse 2011 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Che 2017

Study characteristics	
Patient Sampling	Cross-sectional, prospective, and consecutive
Patient characteristics and setting	Presenting signs and symptoms: patients with evidence of pleural effusion demonstrated by X-ray, suspected to have tuberculosis pleurisy Age: median 44 years, range 18 to 83 years Sex, female: 31% Children: no HIV infection: 1% Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 78 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no

Che 2017 *(Continued)*

	Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: not reported Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Che 2017 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Chen 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients who had symptoms suggestive of urinary tract TB or a urine abnormality Age: mean 53 years (range, 19 to 85) Sex, female: 55% Children: no HIV infection: 0% Clinical setting: multicentre, hospital-based Past history of TB: 31% Participants on anti-TB treatment: no Number of specimens evaluated: 302 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF

Chen 2019 *(Continued)*

	WHO SOP or manufacturer's protocol followed: yes		
Target condition and reference standard(s)	Genitourinary TB MGIT; CRS: culture or positive cystoscopy biopsy, or radiological signs Speciation: yes Decontamination: yes		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Chen 2019 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Chin 2019

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected TB meningitis admitted to the neurology ward Age: adults, range 20 to 41 years Sex, female: not reported Children: not reported HIV infection: 18% Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Participants on anti-TB treatment: 1 participant had received treatment Number of specimens evaluated: 11 Laboratory level: central Country: Uganda World Bank Income Classification: low High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF and Xpert Ultra

Chin 2019 *(Continued)*

	WHO SOP or manufacturer's protocol followed: no
Target condition and reference standard(s)	TB meningitis MGIT Speciation: not reported Decontamination:no
Flow and timing	
Comparative	
Notes	"CSF (2 ml) should be slowly pipetted directly into the Xpert Ultra cartridge. CSF should only be diluted with the manufacturer-supplied sample reagent if less than 2 ml of CSF are available for Xpert Ultra testing." See the following article for full description of CSF processing details, Chin 2019a.

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Chin 2019 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Christopher 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: clinical symptoms and radiographic evidence of a pleural effusion Age: median 46 years (IQR 33 to 57) Sex, female: 20% Children: no HIV infection: not reported Clinical setting: tertiary care centre (Inpatient and outpatient) Past history of TB: yes, 18% Patients on anti-TB treatment: not reported Number of specimens evaluated against culture: 142

Christopher 2013 *(Continued)*

	Number of specimens evaluated against composite reference standard: 146 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for pleural tissue, no for pleural fluid Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: not reported Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Christopher 2013 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Cresswell 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with headache and objective meningism Age: median age 35 years (IQR 30 to 42) Sex, female: 39% Children: no HIV infection: 4% Clinical setting: inpatient Past history of TB: not reported

Cresswell 2018 *(Continued)*

	Participants on anti-TB treatment: not reported Number of specimens evaluated: 118 Laboratory level: central Country: Uganda World Bank Income Classification: low income High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: not reported
Target condition and reference standard(s)	TB meningitis MGIT Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	Additonal information at clinicaltrials.gov/ct2/show/NCT01075152

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Cresswell 2018 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Unclear
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Cresswell 2020

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected meningitis (headache for > 3 days or altered mental status (Glasgow Coma Scale < 15) with clinical signs of meningism at examination, i.e. neck stiffness or Kernig's sign Age: median age 32 years (29 to 38) Sex, female: 42.6% Children: no HIV infection: 96% Clinical setting: inpatient

Cresswell 2020 *(Continued)*

	Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 204 Laboratory level: central Country: Uganda World Bank Income Classification: low income High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIFand Xpert Ultra WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	TB meningitis MGIT Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	No		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Cresswell 2020 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Dhasmana 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: all participants undergoing endobronchial ultrasound (EBUS) for mediastinal lymphadenopathy

Dhasmana 2014 *(Continued)*

	Age: median 46 years, range 14 to 85 years Sex, female: 37% Children: no HIV infection: 7% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 116 Laboratory level: central Country: United Kingdom World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Dhasmana 2014 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Dhooria 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, retrospective

Dhooria 2016 *(Continued)*

Patient characteristics and setting	Presenting signs and symptoms: patients with enlarged mediastinal or hilar lymph nodes (≥ 1 cm in short axis) on computed tomography of the chest who underwent EBUS-guided transbronchial needle aspiration Age: median 40 years, range 30 to 53 years Sex, female: 43% Children: no HIV infection: 0% Clinical setting: tertiary care centre (outpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 147 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: not reported Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Dhooria 2016 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Donovan 2020

Study characteristics			
Patient Sampling	Cross-sectional, random, prospective		
Patient characteristics and setting	Presenting signs and symptoms: patients aged 16 years or older with suspected tuberculous meningitis based on clinical and CSF findings (clear or mildly cloudy CSF, plus > 5 days of symptoms consistent with tuberculous meningitis8 or low CSF glucose or raised CSF lactate concentrations) Age: median age 42 (31 to 57) Sex, female: 40% Children: no HIV infection: 17% Clinical setting: inpatient Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 205 Laboratory level: central Country: Vietnam World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: no High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: yes		
Target condition and reference standard(s)	TB meningitis MGIT Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Donovan 2020 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			

Donovan 2020 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Du 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients found to be smear-negative on prior testing with radiographic evidence of pleural effusion and those subsequently undergoing thoracocentesis and pleural biopsy Age: mean 39 years, SD 13 Sex, female: 44% Children: 0% HIV infection: 4% Clinical setting: 4 tertiary care centres (inpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 126 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes

Du 2015 *(Continued)*

	Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes	Study included specimens found to be smear-negative on prior testing. In the present study, 4 specimens were smear-positive specimens for pleural fluid and 15 were smear-positive for pleural tissue The reference standard for both pleural fluid and pleural tissue was pleural biopsy culture		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		

Du 2015 *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

El-Din 2019

Study characteristics	
Patient Sampling	Cross-sectional. consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected pleural TB based on clinical history and radiologic evidence of pleural effusion Age: 32.7 years ± 13.6 Sex, female: 31% Children: no HIV infection: not reported Clinical setting: not reported Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: not reported Laboratory level: not reported Country: Egypt World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF Specimens processed according to manufacturer's instructions

El-Din 2019 *(Continued)*

Target condition and reference standard(s)	Pleural TB Confirmed TB was defined if acid-fast bacilli were detected by any mean (microscopic evaluation/mycobacterial culture (type not reported)) of either pleural tissue or pleural fluid Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		

El-Din 2019 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Unclear
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Feasey 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected patients with clinical suspicion of tuberculosis Age: mean 37 years, SD 11 years Sex, female: 33% Children: no HIV infection: 100% Clinical setting: tertiary care centre Past history of TB: no Patients on anti-TB treatment: no Number of specimens evaluated: 74 Laboratory level: central Country: Malawi World Bank Income Classification: low income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no

Feasey 2013 *(Continued)*

	Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: disseminated TB (blood) Reference standard for TB detection: Bactec Myco/F Lytic culture Reference standard for rifampicin resistance: not reported Speciation: yes Decontamination: yes, NALC-NaOH for sputum specimens		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Feasey 2013 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Friedrich 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with undiagnosed pleural effusion and high clinical suspicion of pleural TB Age: not reported Sex, female: 36% Children: 0% HIV infection: 28% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated against culture: 24 Number of specimens evaluated against composite reference standard: 25 Laboratory level: central Country: South Africa World Bank Income Classification: middle income

Friedrich 2011 *(Continued)*

	High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MGIT Speciation: yes Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High

Friedrich 2011 *(Continued)*

DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ghariani 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of TB Age: mean 32 years, range 3 to 79 years Sex, female: 68% Children: 13% HIV infection: no Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: 18% Patients on anti-TB treatment: yes, 3% Number of specimens evaluated: 174 Laboratory level: central Country: Tunisia

Ghariani 2015 *(Continued)*

	World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	

Ghariani 2015 *(Continued)*

Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Gu 2015

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspicion of bone and joint TB Age: median 42 years for TB patients, range 18 to 82 years Sex, female: 54% Children: no HIV infection: not reported Clinical setting: tertiary care centre (inpatient) Past history of TB: not reported Patients on anti-TB treatment: yes, 100% Number of specimens evaluated: 60

Gu 2015 *(Continued)*

	Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: bone and joint TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			High
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Gu 2015 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Hanif 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspicion of TB due to symptoms such as fever, cough or weight loss or both, or because they were not responding to initial therapy for other diseases Age: range 20 to 57 years Sex, female: 39% Children: no HIV infection: no Clinical setting: national reference laboratory Past history of TB: not reported

Hanif 2011 *(Continued)*

	Patients on anti-TB treatment: not reported Number of specimens evaluated: 29 Laboratory level: central Country: Kuwait World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol: yes for lymph node aspirate, pleural fluid, and urine; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: TB meningitis, lymph node TB, pleural TB, genitourinary TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: LJ-DST and MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			

Hanif 2011 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Heemskerk 2018

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients who were offered lumbar puncture as a part of routine care for suspected brain infection Age: ≥ 18 years; median 37 years (IQR 28 to 50) Sex, female: 43% Children: no

Heemskerk 2018 *(Continued)*

	HIV infection: 31% Clinical setting: multicentre, hospital-based (both referral and local) Past history of TB: Participants on anti-TB treatment: Number of specimens evaluated: 610 Laboratory level: central in South Africa Country: South Africa, Vietnam, Indonesia World Bank Income Classification: middle High TB burden: South Africa yes; Vietnam yes; Indonesia yes High TB/HIV burden: South Africa yes; Vietnam no; Indonesia yes High MDR-TB burden: South Africa yes; Vietnam yes; Indonesia yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no (as performed in Nhu 2014)
Target condition and reference standard(s)	TB meningitis CRS: clinical TB meningitis, diagnosis (definite, probable and possible TB meningitis); MGIT (MODS Indonesia) Speciation yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Heemskerk 2018 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Hillemann 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected *M tuberculosis* or nontuberculous mycobacterial infection on the basis of clinical criteria

Hillemann 2011 *(Continued)*

	Age: not reported Sex, female: not reported Children: 5% HIV infection: not reported Clinical setting: national reference laboratory Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 200 Laboratory level: central Country: Germany World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: yes, donation of index test
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, genitourinary TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		

Hillemann 2011 *(Continued)*

Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Iram 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective

Iram 2015 *(Continued)*

Patient characteristics and setting	Presenting signs and symptoms: patients with clinical presentation, radiological findings, and histopathological evidence of extrapulmonary TB Age: mean 37 years, range 10 to 80 years Sex, female: 41% Children: 3% HIV infection: 2% Clinical setting: teaching hospital Past history of TB: 53% Patients on anti-TB treatment: yes, 3% Number of specimens evaluated: 18 Laboratory level: intermediate Country: Pakistan World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: no High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, peritoneal TB Reference standard for TB detection: LJ Reference standard for rifampicin resistance: LJ-DST Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		

Iram 2015 *(Continued)*

Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Kim 2015a

Study characteristics

Kim 2015a *(Continued)*

Patient Sampling	Cross-sectional, consecutive, retrospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: median 59 years (IQR 44 to 71 years) Sex, female: 47% Children: 7% HIV infection: 1% Clinical setting: tertiary care centre Past history of TB: 9% Patients on anti-TB treatment: no Number of specimens evaluated: 1209 Laboratory level: central Country: Korea World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB, pleural TB, TB meningitis, peritoneal TB, pericardial TB, bone and joint TB, genitourinary TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: LJ-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Kim 2015a *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Li 2017

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected extrapulmonary TB Age: mean 48 years (SD 10 years) Sex, female: 39% Children: no HIV infection: not reported Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 414 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for pleural fluid, bone and joint TB fluid, urine, and peritoneal fluid; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, peritoneal TB, bone and joint TB, genitourinary TB Reference standard for TB detection: LJ Reference standard for rifampicin resistance: LJ-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	
Methodological quality	

Li 2017 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Liang 2019

Study characteristics	
Patient Sampling	Cross-sectional, manner of patient selection not reported, retrospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected pleural TB based on standard clinical and radiological criteria, including a persistent cough of 2 weeks or more, unexplained fever for 2 weeks or more, weight loss, and radiological evidence of pleural effusion Age: mainly adult; 12% < 25 years Sex, female: 22% Children: not reported HIV infection: not reported Clinical setting: national TB referral hospital Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 219 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	Pleural TB CRS: clinically diagnosed and microbiologically confirmed
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Liang 2019 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ligthelm 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspicion of lymph node TB Age: < 5 years 4%; 5 to 20 years 13%; > 20 years 83% Sex, female: 58% Children: estimated < 15% HIV infection: 19% Clinical setting: university hospital (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 48 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MTBDR*plus* Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	"It is unlikely that our patient cohort had exacerbated disease compared to patients presenting at primary health care clinics, as these patients are routinely referred from the primary health care clinic to the referral centre for FNAB (fine needle aspiration biopsy)"

Ligthelm 2011 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Ligthelm 2011 *(Continued)*

Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Lusiba 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with suspected pleural TB based on clinical signs and symptoms and radiological evidence of a pleural effusion that was considered large enough for a pleural biopsy Age: mean 34 years, SD 13 years Sex, female: 43% Children: no HIV infection: 45% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 116 Laboratory level: central Country: Uganda World Bank Income Classification: low income High TB burden: no High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: LJ and MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: not reported Decontamination: no

Lusiba 2014 *(Continued)*

Flow and timing
Comparative
Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			

Lusiba 2014 *(Continued)*

Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Malbruny 2011

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection by convenience, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of TB Age: median 52 years Sex, female: 40% Children: 7% HIV infection: not reported Clinical setting: university hospital Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 67 Laboratory level: central Country: France World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, bone and joint TB, peritoneal TB, genitourinary TB Reference standard for TB detection: MGIT and Coletsos slants Reference standard for rifampicin resistance: MGIT-DST

Malbruny 2011 *(Continued)*

	Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	No		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	

Malbruny 2011 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Meldau 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients presumed to have pleural TB with any symptoms, including cough, fever, night sweats, loss of weight, haemoptysis, and chest pain, along with features consistent with a pleural effusion on chest X-ray Age: definitive TB: median 39 years (IQR 29 to 55 years); non-TB: median 61 years (IQR 54 to 69 years) Sex, female: 40% Children: no HIV infection: 15% Clinical setting: tertiary care hospital Past history of TB: 13% Patients on anti-TB treatment: no Number of specimens evaluated against culture: 76 Number of specimens evaluated against a composite reference standard: 88 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF

Meldau 2014 *(Continued)*

	WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: pleural TB Reference standard for TB detection: MGIT Reference standard for rifampicin resistance: MGIT-DST Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Meldau 2014 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Meldau 2019

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with any TB symptoms including any cough, fever, night sweats, loss of weight, haemoptysis or chest pain or both, and features consistent with a pleural effusion on chest x-ray Age: Adult; median 39 years (IQR 28 to 57) Sex, female: 11% Children: not reported HIV infection: definite TB: 7% Clinical setting: tertiary care hospital Past history of TB: 6% Participants on anti-TB treatment: not reported Number of specimens evaluated: 149 Laboratory level: central Country: South Africa World Bank Income Classification: middle High TB burden: yes

Meldau 2019 *(Continued)*

	High TB/HIV burden: yes High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: yes		
Target condition and reference standard(s)	Pleural tuberculosis Composite reference standard: MGIT culture and/or histology		
Flow and timing			
Comparative			
Notes			

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Meldau 2019 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Metcalf 2018

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients presenting with a suspected diagnosis of TB meningitis Age: 18 and older Sex, female: 27% Children: No HIV infection: 62% Clinical setting: inpatient Past history of TB: 30% Participants on anti-TB treatment: no Number of specimens evaluated: 37

Metcalf 2018 *(Continued)*

	Laboratory level: central Country: Peru World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes		
Target condition and reference standard(s)	TB meningitis MGIT, Ogawa Speciation: not reported		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Metcalf 2018 *(Continued)*

DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Nataraj 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of extrapulmonary TB Age: < 14 years 13%; 15 to 45 years 52%; > 45 years 34%; range 2 months to 78 years Sex, female: 44% Children: 13% HIV infection: not reported Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 494 Laboratory level: intermediate Country: India

Nataraj 2016 *(Continued)*

	World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, bone and joint TB, genitourinary TB Reference standard TB detection: LJ Reference standard rifampicin resistance detection: LJ-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	Patients on treatment may have been included, although the number was not reported: "Of the two specimens that were smear-positive and smear-negative on both culture and Xpert, one was pleural fluid from a patient who had been receiving Category II anti-tuberculosis treatment for 2 months and the other was pus aspirated from an axillary lymph node"

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Nataraj 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Nhu 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients suspected of having TB meningitis with at least 5 days of meningitis symptoms, nuchal rigidity, and CSF abnormalities Age: > 18 years Sex, female: not reported Children: no HIV infection: 21% Clinical setting: university hospital

Nhu 2014 *(Continued)*

	Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 379 Laboratory level: central Country: Vietnam World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: no High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: yes, donation of index test		
Target condition and reference standard(s)	Target condition: TB meningitis Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST and MTBDR*plus* Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes	Analysis by uniform case definition also included		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			

Nhu 2014 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Ozkutuk 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: median 54 years, range 1 to 99 years Sex, female: 47% Children: 3% HIV infection: not reported

Ozkutuk 2014 *(Continued)*

	Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 1022 Laboratory level: central Country: Turkey World Bank Income Classification: middle High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, genitourinary TB, bone and joint TB, pericardial TB, peritoneal TB Reference standard TB detection: LJ and MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	

Ozkutuk 2014 *(Continued)*

Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Pandie 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with presence of a large pericardial effusion amenable to safe pericardiocentesis (> 10 mm echo-free space around the heart in diastole)

Pandie 2014 *(Continued)*

	Age: median 34 years (IQR 29 to 42) Sex, female: 38% Children: no HIV infection: 74% Clinical setting: 4 district hospitals and 1 tertiary centre (inpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 134 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: pericardial TB Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MTBDR*plus* Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Pandie 2014 *(Continued)*

Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Patel 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of meningitis

Patel 2013 *(Continued)*

	Age: mean 33 years (SD 9) Sex, female: 61% Children: 2% HIV infection: 87% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: 31% Patients on anti-TB treatment: no Number of specimens evaluated: 59 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: TB meningitis Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: no		
Flow and timing			
Comparative			
Notes	Study used frozen specimens		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		

Patel 2013 *(Continued)*

Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Peñata 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective and retrospective

Peñata 2016 *(Continued)*

Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of extrapulmonary tuberculosis Age: mean 42 years (SD 19), range 1 to 91 years Sex, female: 39% Children: 7% HIV infection: 40% Clinical setting: university hospital Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 236 Laboratory level: intermediate Country: Colombia World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB, pleural TB, TB meningitis, peritoneal TB, pericardial TB, bone and joint TB Reference standard TB detection: Ogawa medium Reference standard rifampicin resistance detection: Ogawa-DST Speciation: not reported Decontamination: unclear
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			

Peñata 2016 *(Continued)*

Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Perez-Risco 2018

Study characteristics	
Patient Sampling	Study design unclear, manner of patient selection not reported, retrospective
Patient characteristics and setting	Presenting signs and symptoms: Smear-negative extrapulmonary patients Age: adult Sex, female: not reported Children: 0% HIV infection: not reported Clinical setting: laboratory-based evaluation Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: CSF 3; pleural fluid 24; urine 24; bone or joint fluid 24 Laboratory level: central Country: Spain World Bank Income Classification: high High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert Ultra WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	Target condition: TB meningitis, pleural TB, genitourinary TB, bone or joint TB Reference standard TB detection: MGIT and LJ culture Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	The specimens were collected between May 1999 and May 2017; frozen specimens

Methodological quality

Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**

Perez-Risco 2018 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Unclear		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Rakotoarivelo 2018

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with a febrile illness and chronic respiratory symptoms, pleural effusion, chronic abdominal pain or ascites, chronic meningitis, or other symptoms suggestive of extrapulmonary TB Age: adult; mean (SD) 38.7 years (15.2) Sex, female: 36% Children: no HIV infection: 12% Clinical setting: tertiary care centre Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: CSF: 77; pleural: 50 Laboratory level: central Country: Madagascar World Bank Income Classification: low income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	TB meningitis; pleural TB Reference standard: LJ Composite reference standard: proven and probable cases (culture-positive cases or clinical response to anti-TB treatment without any other diagnosis or other treatment) Speciaiton: yes decontamination: yes
Flow and timing	
Comparative	
Notes	The criteria of Marais were used for the diagnosis of tuberculous meningitis (Marais 2010). This classification and stratification of cases was independent of Xpert MTB/RIF and the panel was blinded to these results.

Rakotoarivelo 2018 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Rakotoarivelo 2018 *(Continued)*

Were all patients included in the analysis?	Yes
Could the patient flow have introduced bias?	Low risk

Rufai 2015

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with high suspicion of pleural TB. Enrolment was based on standard clinical and radiological criteria, including a persistent cough of 2 weeks or longer, unexplained fever for 2 weeks or longer, unexplained weight loss with or without night sweats, chest pain, and radiological evidence of pleural effusion Age: men: mean 42 years (SD 19 years); women: mean 39 years (SD 19 years) Sex, female: 28% Children: 6% HIV infection: no Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 161 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes

Rufai 2015 *(Continued)*

	Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern

Rufai 2015 *(Continued)*

DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Rufai 2017a

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical or radiological suspicion of abdominal TB Age: men: mean 41 years (SD 19 years); women: mean 46 years (SD 20 years) Sex, female: 36% Children: no HIV infection: no Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 67 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: peritoneal TB Reference standard TB detection: MGIT

Rufai 2017a *(Continued)*

	Reference standard rifampicin resistance detection: MGIT-DST Decontamination: yes, NALC-NaOH Speciation: yes
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	

Rufai 2017a *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Rufai 2017b

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: fatigue, malaise, low-grade fever, confusion, nausea and vomiting, lethargy, irritability, and unconsciousness Age: men: mean 38 years (SD 10 years); women: mean 34 years (SD 22 years) Sex, female: 41% Children: 6% HIV infection: not reported Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: yes, 4% Number of specimens evaluated: 267 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no

Rufai 2017b *(Continued)*

Target condition and reference standard(s)	Target condition: TB meningitis Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		

Rufai 2017b *(Continued)*

Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk
Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Safianowska 2012

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: not reported Sex, female: 46% Children: no HIV infection: no Clinical setting: university hospital Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 51 Laboratory level: intermediate Country: Poland World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no

Safianowska 2012 *(Continued)*

Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, peritoneal TB, pericardial TB, genitourinary TB, bone and joint TB Reference standard TB detection: LJ Reference standard rifampicin resistance detection: LJ-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		

Safianowska 2012 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sarfaraz 2018

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients presenting with 1 or more superficial lymph nodes (i.e. cervical, axillary, and inguinal nodes) measuring > 2 cm in largest diameter and persisting for more than 1 month, with or without constitutional symptoms of fever, anorexia, and weight loss Age: > 14 years of age; median 23 years (IQR 18 to 32) Sex, female: 79% Children: no HIV infection: 1% Clinical setting: outpatient Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 261 Laboratory level: central Country: Pakistan World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: no

Sarfaraz 2018 *(Continued)*

	High MDR-TB burden: yes		
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes		
Target condition and reference standard(s)	Lymph node TB, tissue MGIT; LJ Composite reference standard includes histopathology Rifampicin resistance MGIT-DST Speciation: not reported Decontamination: yes (NALC–NaOH)		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			

Sarfaraz 2018 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Scott 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: not reported Age: median 39 years, range < 1 year to 96 years Sex, female: 45% Children: 4% HIV infection: not reported Clinical setting: reference laboratory Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 696 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes

Scott 2014 *(Continued)*

	High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for lymph node aspirate, pleural fluid, and peritoneal fluid; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, peritoneal TB Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST and MTBDR*plus* Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern

Scott 2014 *(Continued)*

DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sharma 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with clinical suspicion of EPTB Age: mean 35 years (SD 15 years) Sex, female: 50% Children: no HIV infection: not reported Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 1139 Laboratory level: central Country: India

Sharma 2014 *(Continued)*

	World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol: yes for body fluids and LN tissue; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, peritoneal TB, pericardial TB, genitourinary TB Reference standard TB detection: LJ and MGIT Reference standard rifampicin resistance detection: LJ-DST Speciation: yes Decontamination: yes, NALC-NaOH (for all specimens except CSF, pleural fluid, and urine)
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Sharma 2014 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sharma 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: women being evaluated for infertility and suspected to have TB Age: mean 29 years, range 19 to 41 years Sex, female: 100% Children: no HIV infection: not reported Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no

Sharma 2016 *(Continued)*

	Number of specimens evaluated: 240 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: genitourinary TB Reference standard TB detection: LJ and MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Sharma 2016 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sharma 2018

Study characteristics	
Patient Sampling	Cross-sectional, random selection, prospective
Patient characteristics and setting	Presenting signs and symptoms: participants with persistent cough and unexplained fever for 2 weeks or more, unexplained weight loss, pleuritic chest pain, anorexia – among others, positive Mantoux test and the suggestive radiological findings Age: mean 39 years (range, 18 to 60) Sex, female: 64% Children: no HIV infection: 0% Clinical setting: university hospital

Sharma 2018 *(Continued)*

	Past history of TB: Participants on anti-TB treatment: no Number of specimens evaluated: 78 Laboratory level: central Country: India World Bank Income Classification: middle-income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol: yes
Target condition and reference standard(s)	Pleural tuberculosis, pleural fluid Composite reference standard: combination of smear, culture, clinical findings, radiology, histology, cytology, response to ATT Speciation: yes decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		

Sharma 2018 *(Continued)*

If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Siddiqi 2019

Study characteristics	
Patient Sampling	Cohort, manner of patient selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: presented with signs and symptoms concerning for TB meningitis and already received a lumbar puncture as part of routine care Age: age 18 years and older; TB meningitis culture positive: median 35 years (IQR 30 to 41) Sex, female: 36% Children: no HIV infection: 86% Clinical setting: university teaching hospital

Siddiqi 2019 *(Continued)*

	Past history of TB: 20% Participants on anti-TB treatment: not reported Number of specimens evaluated: 550 Laboratory level: central Country: Zambia World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	TB meningitis MGIT Rifampicin resistance Samples found to be rifampin resistant by Xpert MTB/RIF had confirmatory DST for rifampin and isoniazid conducted separately Speciation: yes Decontamination: No
Flow and timing	
Comparative	
Notes	After a lumbar puncture was completed, study staff identified patients from the microbiology laboratories who had 3 ml of excess CSF remaining after routine testing composed of Gram stain, India ink stain, cryptococcal antigen testing, and bacterial culture on a blood agar plate. A composite reference standard was defined as probable TB meningitis = patients with a CSF white blood cell count between 10 and 500, CSF total protein of 100 mg/dl, and CSF glucose of 40 mg/dl. These values were adapted from a uniform case definition of probable TBM for use in clinical research (Marais 2010). However, sensitivity and specificity were only determined using culture as the reference standard

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		

Siddiqi 2019 *(Continued)*

Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Sun 2019

Study characteristics

Sun 2019 *(Continued)*

Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with symptoms such as pain, swelling in the joints, tenderness, effusion, restriction of movements, and systematic symptoms such as fever, loss of weight/appetite, elevated erythrocyte sedimentation rate, and cough, breathlessness, and history of TB Age: osteoarticular TB: median 51 years (range 16 to 86) Sex, female: osteoarticular TB: 55% Children: no HIV infection: 0% Clinical setting: national level TB referral centre Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 166 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: yes
Target condition and reference standard(s)	Bone or joint TB, fluid MGIT Composite reference standard: clinical, laboratory, histopathological, radiological and ≥ 6 months' follow-up Rifampicin resistance LJ-DST Speciation: yes Decontamination: Yes
Flow and timing	
Comparative	
Notes	

Sun 2019 *(Continued)*

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	

Sun 2019 *(Continued)*

Are there concerns that the target condition as defined by the reference standard does not match the question?		Low concern
DOMAIN 4: Flow and Timing		
Was there an appropriate interval between index test and reference standard?	Yes	
Did all patients receive the same reference standard?	Yes	
Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Suzana 2016

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with signs and symptoms suggestive of extrapulmonary TB Age: median 34 years Sex, female: 39% Children: 0.06% HIV infection: 7% Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 215 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for lymph node tissue and pleural tissue; no for pleural fluid, bone and joint fluid, urine, peritoneal fluid, pericardial fluid, and CSF Manufacturer's involvement: no

Suzana 2016 *(Continued)*

Target condition and reference standard(s)	Target condition: pleural TB, lymph node TB, TB meningitis, peritoneal TB, pericardial TB, genitourinary TB, bone and joint TB Reference standard TB detection: LJ and MGIT Reference standard rifampicin resistance detection: LJ-DST and MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Suzana 2016 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Tadesse 2015

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: people with presumptive lymph node TB Age: ≤ 15 years 15%; > 15 years 85% Sex, female: 53% Children: 15% HIV infection: not reported Clinical setting: university hospital (outpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 136 Laboratory level: central Country: Ethiopia World Bank Income Classification: low income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes

Tadesse 2015 *(Continued)*

	Manufacturer's involvement: no		
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard TB detection: LJ Reference standard rifampicin resistance detection: not reported Speciation: yes Decontamination: yes, NALC-NaOH		
Flow and timing			
Comparative			
Notes	Study used frozen specimens		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		

Tadesse 2015 *(Continued)*

For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Trajman 2014

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients with a pleural effusion needing thoracentesis Age: median 50 years (IQR 40 to 57) Sex, female: 20% Children: no HIV infection: 5% Clinical setting: secondary health facility (inpatient) Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 85 Laboratory level: central Country: Brazil World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes

Trajman 2014 *(Continued)*

	Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	Patients were excluded if they had bleeding disorders contraindicating thoracentesis, if the fluid volume was insufficient for storage, or if a final diagnosis could not be ascertained. One of the main limitations of the study was the high number of presumptive (non-confirmed) cases. The number of exclusions was also high: out of 203 eligible patients, 110 were excluded: 21 did not have a final diagnosis and 89 did not have sufficient fluid to store. "Cultures of pleural tissue, which could significantly improve accuracy of diagnosis, were not performed" Study used frozen specimens

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Low concern
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			

Trajman 2014 *(Continued)*

DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Unclear		
Were all patients included in the analysis?	No		
Could the patient flow have introduced bias?		High risk	

Ullah 2017

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients meeting the following criteria: previously TB-treated cases with both positive and negative smears; failure of Cat-I and Cat-II TB drugs; all smear-positive cases that remained positive by the end of the second month of TB treatment; TB/HIV co-infection cases; seriously ill patients; contacts of MDR-TB patients Age: mean 34 years (SD 19 years), range 3 to 80 years Sex, female: 51% Children: 14% HIV infection: not reported Clinical setting: tertiary care centre Past history of TB: 60% Patients on anti-TB treatment: yes, percentage not reported Number of specimens evaluated: 168

Ullah 2017 *(Continued)*

	Laboratory level: central Country: Pakistan World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: no High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB, TB meningitis, peritoneal TB, pericardial TB Reference standard TB detection: Middlebrook 7H10 Reference standard rifampicin resistance detection: Middlebrook 7H10 Speciation: not reported Decontamination: no
Flow and timing	
Comparative	
Notes	Study included a highly selective population that met specified criteria: previously TB-treated cases with both positive and negative smears; failure of Cat-I and Cat-II TB drugs; all smear-positive cases that remained positive by the end of the second month of TB treatment; TB/HIV co-infection cases; seriously ill patients; contacts of MDR-TB patients

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		High risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			

Ullah 2017 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Vadwai 2011

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: suspected extrapulmonary TB based on symptoms: brain: irritability, restlessness, neck stiffness, headache persistent for 2 to 3 weeks, vomiting, seizures, changes in mental condition or behaviour; intestinal tract, abdomen: abdominal pain, diarrhoea; lymph nodes: enlargement of lymph nodes, mass formation in the neck; cardiorespiratory: shortness of breath, hypertension, chest pain, dyspnoea;

Vadwai 2011 *(Continued)*

	endometrium: pelvic pain, pelvic mass, irregular periods, infertility; skin (cutaneous): visible presence of ulcers or lesions, tender nodules Age: median 37 years Sex, female: 15% Children: 3% HIV infection: 3% Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 60 Laboratory level: central Country: India World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for pleural fluid, peritoneal fluid, pericardial fluid; no for CSF Manufacturer's involvement: yes, in design, analysis, or manuscript production (David Alland is among a group of co-investigators who invented molecular beacons and receive income from licensees, including to Cepheid, for *M tuberculosis* detection)
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, peritoneal TB, pericardial TB Reference standard TB detection: LJ and MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: yes, NALC-NaOH
Flow and timing	
Comparative	
Notes	"Patients were enrolled only if they could provide detailed clinical history and radiological and histology/cytology reports, along with an adequate amount of specimen material"

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Vadwai 2011 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Unclear		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Vadwai 2011 *(Continued)*

Could the patient flow have introduced bias?	Low risk

Van Rie 2013

Study characteristics	
Patient Sampling	Cross-sectional, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: HIV-infected patients with suspicion of LNTB Age: mean 36 years, range 18 to 73 years Sex, female: 49% Children: no HIV infection: 100% Clinical setting: tertiary care centre (inpatient and outpatient) Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 344 Laboratory level: central Country: South Africa World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: lymph node TB Reference standard TB detection: MGIT Reference standard rifampicin resistance detection: MGIT-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	

Van Rie 2013 *(Continued)*

Notes

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		

Van Rie 2013 *(Continued)*

Were all patients included in the analysis?	Yes	
Could the patient flow have introduced bias?		Low risk

Wang 2019

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: adults who were offered lumbar puncture as a part of routine care for suspected brain infection; TB symptoms, chest pain, radiological evidence of pleural effusion, thoracoscopic examination that suggested TB Age: 15 years and older; pleural tuberculosis TB 37 years (range, 15 to 89); TB meningitis 33 years (range, 15 to 83) Sex, female: pleural tuberculosis: 20%; TB meningitis: 44% Children: no HIV infection: 0% Clinical setting: national level tuberculosis referral centre Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: not reported Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes Prevalence of TB cases in the study:
Index tests	Xpert MTB/RIF and Xpert Ultra
Target condition and reference standard(s)	LJ and MGIT Composite reference standard for pleural TB: composed of clinical, laboratory, histopathological, and radiological and follow-up features Rifampicin resistance LJ-DST

Wang 2019 *(Continued)*

	Speciation: not reported Decontamination: no		
Flow and timing			
Comparative			
Notes			
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		

Wang 2019 *(Continued)*

Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Unclear		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Wang 2020

Study characteristics	
Patient Sampling	Cohort, consecutive, prospective
Patient characteristics and setting	Presenting signs and symptoms: suspected pleural tuberculosis Age: median 45 years; range: 15 to 89 Sex, female: 32.5% Children: no HIV infection: 0% Clinical setting: Unclear Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: 139 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden country: yes High MDR-TB burden country: yes High TB/HIV burden country: yes

Wang 2020 *(Continued)*

Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: yes Manufacturer's involvement: no		
Target condition and reference standard(s)	Pleural TB LJ and MGIT Speciation: Yes Decontamination: no		
Flow and timing			
Comparative			
Notes	This study used fresh specimens for Xpert and frozen specimens for Xpert Ultra		
Methodological quality			
Item	**Authors' judgement**	**Risk of bias**	**Applicability concerns**
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	No		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?			
If a threshold was used, was it pre-specified?			
Could the conduct or interpretation of the index test have introduced bias?			
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		

Wang 2020 *(Continued)*

Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Unclear		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	Yes		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Unclear risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Wu 2019

Study characteristics	
Patient Sampling	Cohort, manner of selection not reported, consecutive
Patient characteristics and setting	Presenting signs and symptoms: patients with suspicion of extrapulmonary tuberculosis; diagnostic criteria followed the WHO guidelines and was based on a combination of clinical symptoms, radiological evidence compatible with active TB, histological observations, lack of improvement in response to a course of broad-spectrum antibiotics Age: 16 years and older Sex, female: 32% Children: no HIV infection: 0% Clinical setting: tertiary-care hospital

Wu 2019 *(Continued)*

	Past history of TB: not reported Participants on anti-TB treatment: not reported Number of specimens evaluated: lymph node fluid 52; pleural fluid: 119 Laboratory level: central Country: China World Bank Income Classification: middle income High TB burden: yes High TB/HIV burden: yes High MDR-TB burden: yes
Index tests	Xpert MTB/RIF and Xpert Ultra WHO SOP or manufacturer's protocol followed: no (see note)
Target condition and reference standard(s)	Lymph node tuberculosis; pleural tuberculosis MGIT Speciation: not reported Sterile specimens were directly processed. Non-sterile specimens were pretreated with N-acetyl-L-cysteine-NaOH-Na citrate
Flow and timing	
Comparative	
Notes	4 ml GeneXpert sample reagent was added to the remaining 1 ml of each specimen

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			

Wu 2019 *(Continued)*

Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?			
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Unclear
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Zeka 2011

Study characteristics

Zeka 2011 *(Continued)*

Patient Sampling	Cross-sectional, consecutive, retrospective
Patient characteristics and setting	Presenting signs and symptoms: clinical findings of possible TB Age: median 48 years Sex, female: 42% Children: 13% HIV infection: 1% Clinical setting: tertiary care centre Past history of TB: not reported Patients on anti-TB treatment: no Number of specimens evaluated: 149 Laboratory level: central Country: Turkey World Bank Income Classification: middle income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: no Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, genitourinary TB, peritoneal TB, pericardial TB Reference standard TB detection: LJ and BacT liquid medium Reference standard rifampicin resistance detection: 7H10 agar media Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	Study used frozen specimens

Methodological quality

Item	Authors' judgement	Risk of bias	Applicability concerns

Zeka 2011 *(Continued)*

DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Yes		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Low risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			High
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	Yes		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		Low risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		
Could the patient flow have introduced bias?		Low risk	

Zmak 2013

Study characteristics	
Patient Sampling	Cross-sectional, manner of participant selection not reported, prospective
Patient characteristics and setting	Presenting signs and symptoms: patients suspected of EPTB Age: 15 years and older Sex, female: not reported Children: 13% HIV infection: not reported Clinical setting: laboratory-based evaluation Past history of TB: not reported Patients on anti-TB treatment: not reported Number of specimens evaluated: 176 Laboratory level: central Country: Croatia World Bank Income Classification: high income High TB burden: no High TB/HIV burden: no High MDR-TB burden: no
Index tests	Xpert MTB/RIF WHO SOP or manufacturer's protocol followed: yes for pleural fluid, urine, peritoneal fluid, pericardial fluid, and blood; no for CSF Manufacturer's involvement: no
Target condition and reference standard(s)	Target condition: pleural TB, TB meningitis, peritoneal TB, pericardial TB, genitourinary TB, disseminated TB Reference standard TB detection: LJ, Stonebrink, and MGIT Reference standard rifampicin resistance detection: LJ-DST Speciation: yes Decontamination: no
Flow and timing	
Comparative	
Notes	"Although the NRL performs a third-level laboratory service for the whole country, it is actually also involved in first and second-level laboratory work for several counties"
Methodological quality	

Zmak 2013 *(Continued)*

Item	Authors' judgement	Risk of bias	Applicability concerns
DOMAIN 1: Patient Selection			
Was a consecutive or random sample of patients enrolled?	Unclear		
Was a case-control design avoided?	Yes		
Did the study avoid inappropriate exclusions?	Yes		
Could the selection of patients have introduced bias?		Unclear risk	
Are there concerns that the included patients and setting do not match the review question?			Unclear
DOMAIN 2: Index Test (Xpert MTB/RIF)			
Were the index test results interpreted without knowledge of the results of the reference standard?	Yes		
If a threshold was used, was it pre-specified?	Yes		
Could the conduct or interpretation of the index test have introduced bias?		Low risk	
Are there concerns that the index test, its conduct, or interpretation differ from the review question?			Low concern
DOMAIN 2: Index Test (Xpert Ultra)			
DOMAIN 3: Reference Standard			
Is the reference standards likely to correctly classify the target condition?	Yes		
Were the reference standard results interpreted without knowledge of the results of the index tests?	No		
For rifampicin resistance testing, were the reference standard results interpreted without knowledge of the results of the index test?	No		
Could the reference standard, its conduct, or its interpretation have introduced bias?		High risk	
Are there concerns that the target condition as defined by the reference standard does not match the question?			Low concern
DOMAIN 4: Flow and Timing			
Was there an appropriate interval between index test and reference standard?	Yes		
Did all patients receive the same reference standard?	Yes		
Were all patients included in the analysis?	Yes		

Zmak 2013 *(Continued)*

Could the patient flow have introduced bias?	Low risk

CSF: cerebrospinal fluid; DST: drug susceptibility testing; EBUS: endobronchial ultrasound; EPTB: extrapulmonary tuberculosis: IQR: interquartile ratio; LJ: Löwenstein-Jensen; LN: lymph node; MDR-TB: multi-drug-resistant tuberculosis; MGIT: mycobacteria growth indicator tube; NALC-NaOH: N-acetyl-L-cysteine-sodium hydroxide; SD: standard deviation; SOP: standard operating procedure; TB: tuberculosis; TBM: tuberculous meningitis; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abong 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Adejumo 2018	Did not contain specimen for extrapulmonary TB
Afsar 2018	Did not contain data by site for extrapulmonary TB
Ahmad 2018	Inadequate reference standard
Akhter 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Ali 2018	Inadequate reference standard
Allahyartorkaman 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Alvarez Uria 2012	Inappropriate reference standard
Andrey 2015	Case report
Armand 2011	Case-control study
Arockiaraj 2015	Abstract; we included the published study (Arockiaraj 2017) in the review
Arockiaraj 2017	Includes both adults and children or no information about age of enrolment
Arockiaraj 2019a	Case-control study
Arockiaraj 2019b	Children
Atherton 2018	Case report
Aydemir 2019	Could not obtain; same publication as Terzi 2019
Bablishvili 2015	Did not contain specimen for extrapulmonary TB
Bahr 2018a	Test other than Xpert MTB/RIF and Xpert Ultra
Bahr 2018b	Duplicate data for Bahr 2017
Bahr 2019	Review
Baikunje 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Bajrami 2016	Could not extract 2 × 2 values

Study	Reason for exclusion
Balcha 2014	Did not contain specimen for extrapulmonary TB
Bankar 2018	Includes both adults and children or no information about age of enrolment
Bemba 2017	Inappropriate reference standard
Ben Saad 2018	Could not extract 2 × 2 values
Bhardwaj 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Bhatia 2016	Could not extract 2 × 2 values
Bholla 2016	Children
Biadglegne 2013	Could not extract 2 × 2 values
Bilgin 2016	Could not extract 2 × 2 values
Borraz-Noriega 2018	Could not extract 2 × 2 values
Boyles 2018	Correspondence without original data
Bunsow 2014	Could not extract 2 × 2 values
Celik 2015	Could not extract 2 × 2 values
Chaidir 2018	Inappropriate reference standard
Chakraborty 2019	Xpert Ultra was not evaluated
Chen 2016	Could not extract 2 × 2 values
Chhajed 2019	Xpert Ultra was not evaluated
Christopher 2018	Could not extract 2 x 2 values
Coetzee 2014	Children
Coleman 2015	Case-control study
Creswell 2019	Did not contain specimen for extrapulmonary TB
Dahale 2019	Case-control study
Das 2019	Children
Deggim 2013	Fewer than 5 specimens for a given type of specimen (only 1 pleural fluid specimen)
Dharan 2016	Did not contain specimen for extrapulmonary TB
Diallo 2016	Includes both adults and children or no information about age of enrolment
Diop 2016	Inappropriate reference standard
Edwards 2016	Case report

Study	Reason for exclusion
Ejeta 2018	Could not extract 2 x 2 values
Erdem 2014	Index test other than Xpert MTB/RIF
Fanosie 2016	Did not contain specimen for extrapulmonary TB
Fantahun 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Floridia 2017	Could not extract 2 x 2 values
García 2017	Duplicate data for García Cañete 2017
García Cañete 2017	Includes both adults and children or no information about age of enrolment
Gascoyne-Binzi 2012	Abstract; we could not extract data by form of extrapulmonary TB
Gati 2018	Could not extract 2 x 2 values
Gautam 2018	Inappropriate reference standard
Gautam 2019	Inappropriate reference standard
Gounden 2018	Could not extract 2 x 2 values
Gulla 2019	Could not extract 2 x 2 values
Gursoy 2016	Includes both adults and children or no information about age of enrolment
Habeenzu 2017	Did not contain specimen for extrapulmonary TB
Habous 2019	Includes both adults and children or no information about age of enrolment
Hanifa 2017	Could not extract 2 x 2 values
Held 2014	Bone tissue, specimen not included
Held 2016	Bone tissue, specimen not included
Held 2017	Bone tissue, specimen not included
Ioannidis 2010	Duplicate data
Ioannidis 2011	Includes both adults and children or no information about age of enrolment
Jain 2017	Inappropriate reference standard
Jing 2017	Includes both adults and children or no information about age of enrolment
Jipa 2017	Could not extract 2 x 2 values
Jorstad 2018	Inappropriate reference standard
Joythi 2019	Children
Kanade 2018	Did not contain data by site for extrapulmonary TB

Study	Reason for exclusion
Kashyap 2019	Inappropriate reference standard
Kendall 2019	Case-control study
Kerkhoff 2017	Did not contain specimen for extrapulmonary TB
Khadka 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Khan 2018	Includes both adults and children or no information about age of enrolment
Kilfoil 2015	Could not extract 2 × 2 values
Kim 2014	Could not extract 2 × 2 values; unclear if culture-positive; pleural fluid (3), CSF (2); peritoneal fluid (1)
Kim 2015b	Case-control study
Kim 2015c	Could not extract 2 × 2 values
Kotovich 2018	Inappropriate reference standard
Koul 2018	Could not extract 2 × 2 values
Kumar 2017	Case-control study
Kumari 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Kurbaniyazova 2017	Did not contain specimen for extrapulmonary TB
Kwak 2015	Duplicate data
Lawn 2012	Screening study
Lawn 2013	Could not extract 2 × 2 values
Lawn 2015	Screening study
Lawn 2017	Could not extract 2 × 2 values
Lee 2017	Duplicate data
Lemus-Minor 2018	Did not contain specimen for extrapulmonary TB
Li 2018	Inappropriate reference standard
Li 2020	Test other than Xpert MTB/RIF and Xpert Ultra
Liu 2015	Duplicate data
Liu 2019	Did not contain specimen for extrapulmonary TB
Lombardi 2017	Could not extract data by site of extrapulmonary TB
Marouane 2014	Abstract; we excluded the publication, Marouane 2016, because we could not extract 2 × 2 values

Study	Reason for exclusion
Marouane 2016	Could not extract 2 × 2 values
Massi 2017	Includes both adults and children or no information about age of enrolment
Mathew 2018	Did not contain data by site for extrapulmonary TB
Mazzola 2016	Includes both adults and children or no information about age of enrolment
McMillen 2018	Did not contain data by site for extrapulmonary TB
Mechal 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Metaferia 2018	Could not extract 2 × 2 values
Miller 2011	Fewer than 5 specimens for a given type of specimen; lymph node biopsy (3 specimens, of which 1 was culture-positive) and endometrial biopsy (1 specimen that was culture-positive)
Mishra 2017	Abstract; we did not identify a published study
Moure 2011	Fewer than 5 specimens for a given type of specimen: CSF (3 specimens, all culture-negative); pleural fluid (4 specimens, 2 culture-positive); lymph node aspirate (1 specimen, culture-negative); urine (2 specimens, both culture-positive); peritoneal fluid (2, both culture-negative)
Moure 2012	Case-control study
Negi 2019	Case-control study
Nhu 2013	Inappropriate reference standard
Omar 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Pandey 2017	Includes both adults and children or no information about age of enrolment
Paramitha 2018	Could not extract 2 × 2 values
Park 2019	Inappropriate reference standard
Patel 2014	Duplicate data
Patel 2020	Test other than Xpert MTB/RIF and Xpert Ultra
Peter 2012	Case-control study
Philip 2017	Inappropriate reference standard
Piersimoni 2019	Could not extract 2 x 2 tables
Pink 2016	Includes both adults and children or no information about age of enrolment
Pohl 2016	Children
Porcel 2013	Case-control study
Rachow 2012	Did not contain specimen for extrapulmonary TB

Study	Reason for exclusion
Raizada 2015	Inappropriate reference standard
Raizada 2018	Children
Ramamurthy 2016	Could not extract data by site of extrapulmonary TB
Rathour 2019	Children
Razack 2014	Test other than Xpert MTB/RIF and Xpert Ultra
Rebecca 2018	Children
Reddy 2017	Could not extract 2 × 2 values
Rindi 2017	Case-control study
Rossato Silva 2018	Did not contain specimen for extrapulmonary TB
Ruiz 2017	Did not contain data by site for extrapulmonary TB
Sachdeva 2018	Includes both adults and children or no information about age of enrolment
Saeed 2017a	Includes both adults and children or no information about age of enrolment
Saeed 2017b	Could not extract 2 × 2 values
Saeed 2018	Did not contain data by site for extrapulmonary TB
Salvador 2015	Case-control study
Samuel 2018	Inappropriate reference standard
Sanjuan Jimenez 2015	Case-control study
Schutz 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Sekyere 2019	Could not extract 2 x 2 data
Set 2018	Did not contain data by site for extrapulmonary TB
Set 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Shah 2016a	Case-control study
Shakeel 2018	Did not contain data by site for extrapulmonary TB
Sharma 2017a	Did not contain data by site for extrapulmonary TB
Sharma 2019	Did not include specimen of interest
Singanayagam 2014	Could not extract 2 × 2 values
Singh 2016	Could not extract 2 × 2 values
Smith 2014	Did not contain specimen for extrapulmonary TB

Study	Reason for exclusion
Solomons 2015	Duplicate data
Solomons 2016	Includes both adults and children or no information about age of enrolment
Soomro 2017	Could not extract 2 × 2 values
Sumayya 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Tahseen 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Talib 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Tang 2017	Could not extract 2 × 2 values
Tang 2018	Case-control study
Teo 2011	Includes both adults and children or no information about age of enrolment
Terzi 2019	Could not obtain; same publication as Aydemir 2019
Theron 2014b	Duplicate data
Tortoli 2012	Includes both adults and children or no information about age of enrolment
Toure 2017	Could not extract 2 × 2 values
Uddin 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Vallejo 2015	Could not extract 2 × 2 values
Verghese 2016	Abstract; we did not identify a published study
Wang 2016a	Could not extract 2 × 2 values
Wang 2016b	Includes both adults and children or no information about age of enrolment
Wang 2018	Inadequate reference standard
Wei 2016	Inappropriate reference standard
Yang 2017	Could not obtain 2 x 2 values
Yang 2019	Test other than Xpert MTB/RIF and Xpert Ultra
Yu 2020	Test other than Xpert MTB/RIF and Xpert Ultra
Yuan 2016	Inappropriate reference standard
Zhang 2016	Could not extract 2 × 2 values
Zhou 2020	Test other than Xpert MTB/RIF and Xpert Ultra
Zurcher 2019	Test other than Xpert MTB/RIF and Xpert Ultra

TB: tuberculosis.

DATA

Presented below are all the data for all of the tests entered into the review.

Table Tests. Data tables by test

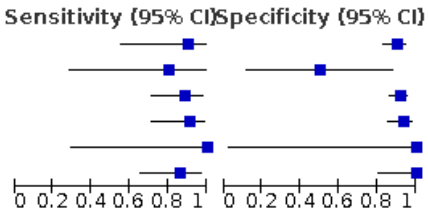
Test	No. of studies	No. of participants
1 Cerebrospinal fluid, Xpert Ultra, culture	6	475
2 Cerebrospinal fluid, Xpert Ultra, composite reference standard	4	496
3 Cerebrospinal fluid, Xpert MTB/RIF, culture	33	3434
4 Cerebrospinal fluid, Xpert MTB/RIF, composite reference standard	14	2203
5 Cerebrospinal fluid, Xpert Ultra, HIV positive	2	333
6 Cerebrospinal fluid, Xpert MTB/RIF, HIV positive	3	413
7 Pleural fluid, Xpert Ultra, culture	4	398
8 Pleural fluid, Xpert Ultra, composite reference standard	2	263
9 Pleural fluid, Xpert MTB/RIF, culture	28	3268
10 Pleural fluid, Xpert MTB/RIF, composite reference standard	10	1024
11 Pleural tissue, Xpert MTB/RIF, culture	4	214
12 Pleural tissue, Xpert MTB/RIF, composite reference standard	1	55
13 Lymph node aspirate, Xpert Ultra, culture	1	73
14 Lymph node aspirate, Xpert Ultra, composite reference standard	1	73
15 Lymph node aspirate, Xpert MTB/RIF, culture	15	1595
16 Lymph node aspirate, Xpert MTB/RIF, composite reference standard	4	679
17 Lymph node biopsy, Xpert Ultra, culture	2	131
18 Lymph node biopsy, Xpert Ultra, composite reference standard	1	79
19 Lymph node biopsy, Xpert MTB/RIF, culture	11	786
20 Lymph node biopsy, Xpert MTB/RIF, composite	2	288
21 Urine, Xpert Ultra, culture	1	24
22 Urine, Xpert MTB/RIF, culture	15	1068
23 Urine, Xpert MTB/RIF, composite reference standard	2	463

Test	No. of studies	No. of participants
24 Bone or joint aspirate, Xpert Ultra, culture	2	94
25 Bone or joint aspirate, Xpert Ultra, composite reference standard	1	145
26 Bone or joint aspirate, Xpert MTB/RIF, culture	12	492
27 Bone or Joint aspirate, Xpert MTB/RIF, composite reference standard	2	205
28 Bone or joint tissue, Xpert MTB/RIF, culture	3	30
29 Peritoneal fluid, Xpert Ultra, culture	1	3
30 Peritoneal fluid, Xpert MTB/RIF, culture	17	619
31 Peritoneal tissue, Xpert MTB/RIF, culture	1	28
32 Pericardial fluid, Xpert MTB/RIF, culture	14	258
33 Pericardial fluid, Xpert MTB/RIF, composite reference standard	2	77
34 Blood, Xpert MTB/RIF, culture	2	85
35 Rifampicin resistance, Xpert Ultra	5	132
36 Rifampicin resistance, Xpert MTB/RIF	33	1246

Test 1. Cerebrospinal fluid, Xpert Ultra, culture

Cerebrospinal fluid, Xpert Ultra, culture

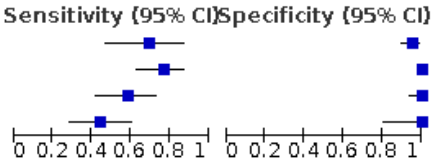
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bahr 2017	9	12	1	107	0.90 [0.55, 1.00]	0.90 [0.83, 0.95]
Chin 2019	4	3	1	3	0.80 [0.28, 0.99]	0.50 [0.12, 0.88]
Cresswell 2020	24	15	3	162	0.89 [0.71, 0.98]	0.92 [0.86, 0.95]
Donovan 2020	20	4	2	62	0.91 [0.71, 0.99]	0.94 [0.85, 0.98]
Perez-Risco 2018	3	0	0	1	1.00 [0.29, 1.00]	1.00 [0.03, 1.00]
Wang 2019	19	0	3	17	0.86 [0.65, 0.97]	1.00 [0.80, 1.00]



Test 2. Cerebrospinal fluid, Xpert Ultra, composite reference standard

Cerebrospinal fluid, Xpert Ultra, composite reference standard

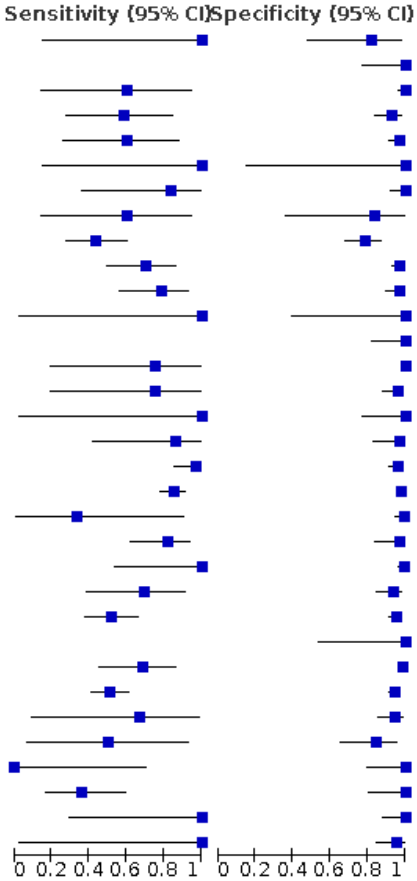
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bahr 2017	16	5	7	101	0.70 [0.47, 0.87]	0.95 [0.89, 0.98]
Cresswell 2020	39	0	12	153	0.76 [0.63, 0.87]	1.00 [0.98, 1.00]
Donovan 2020	25	0	18	60	0.58 [0.42, 0.73]	1.00 [0.94, 1.00]
Wang 2019	19	0	24	17	0.44 [0.29, 0.60]	1.00 [0.80, 1.00]



Test 3. Cerebrospinal fluid, Xpert MTB/RIF, culture

Cerebrospinal fluid, Xpert MTB/RIF, culture

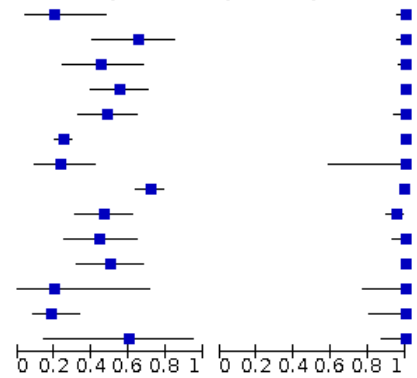
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ajbani 2018	2	2	0	9	1.00 [0.16, 1.00]	0.82 [0.48, 0.98]
Al-Ateah 2012	0	0	0	14	Not estimable	1.00 [0.77, 1.00]
Azevedo 2018	3	0	2	96	0.60 [0.15, 0.95]	1.00 [0.96, 1.00]
Bahr 2015	7	5	5	63	0.58 [0.28, 0.85]	0.93 [0.84, 0.98]
Bahr 2017	6	4	4	115	0.60 [0.26, 0.88]	0.97 [0.92, 0.99]
Blaich 2014	2	0	0	2	1.00 [0.16, 1.00]	1.00 [0.16, 1.00]
Causse 2011	5	0	1	44	0.83 [0.36, 1.00]	1.00 [0.92, 1.00]
Chin 2019	3	1	2	5	0.60 [0.15, 0.95]	0.83 [0.36, 1.00]
Cresswell 2018	17	17	22	62	0.44 [0.28, 0.60]	0.78 [0.68, 0.87]
Cresswell 2020	19	6	8	171	0.70 [0.50, 0.86]	0.97 [0.93, 0.99]
Donovan 2020	18	2	5	63	0.78 [0.56, 0.93]	0.97 [0.89, 1.00]
Hanif 2011	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Hillemann 2011	0	0	0	19	Not estimable	1.00 [0.82, 1.00]
Kim 2015a	3	0	1	250	0.75 [0.19, 0.99]	1.00 [0.99, 1.00]
Li 2017	3	3	1	67	0.75 [0.19, 0.99]	0.96 [0.88, 0.99]
Malbruny 2011	1	0	0	14	1.00 [0.03, 1.00]	1.00 [0.77, 1.00]
Metcalf 2018	6	1	1	29	0.86 [0.42, 1.00]	0.97 [0.83, 1.00]
Nataraj 2016	35	5	1	119	0.97 [0.85, 1.00]	0.96 [0.91, 0.99]
Nhu 2014	103	6	18	252	0.85 [0.78, 0.91]	0.98 [0.95, 0.99]
Ozkutuk 2014	1	1	2	107	0.33 [0.01, 0.91]	0.99 [0.95, 1.00]
Patel 2013	22	1	5	31	0.81 [0.62, 0.94]	0.97 [0.84, 1.00]
Peñata 2016	6	1	0	148	1.00 [0.54, 1.00]	0.99 [0.96, 1.00]
Rakotoarivelo 2018	9	4	4	60	0.69 [0.39, 0.91]	0.94 [0.85, 0.98]
Rufai 2017b	27	11	25	204	0.52 [0.38, 0.66]	0.95 [0.91, 0.97]
Safianowska 2012	0	0	0	6	Not estimable	1.00 [0.54, 1.00]
Sharma 2014	15	3	7	205	0.68 [0.45, 0.86]	0.99 [0.96, 1.00]
Siddiqi 2019	55	26	52	417	0.51 [0.42, 0.61]	0.94 [0.92, 0.96]
Suzana 2016	2	3	1	53	0.67 [0.09, 0.99]	0.95 [0.85, 0.99]
Ullah 2017	2	4	2	22	0.50 [0.07, 0.93]	0.85 [0.65, 0.96]
Vadwai 2011	0	0	3	16	0.00 [0.00, 0.71]	1.00 [0.79, 1.00]
Wang 2019	8	0	14	17	0.36 [0.17, 0.59]	1.00 [0.80, 1.00]
Zeka 2011	3	0	0	28	1.00 [0.29, 1.00]	1.00 [0.88, 1.00]
Zmak 2013	1	2	0	43	1.00 [0.03, 1.00]	0.96 [0.85, 0.99]



Test 4. Cerebrospinal fluid, Xpert MTB/RIF, composite reference standard

Cerebrospinal fluid, Xpert MTB/RIF, composite reference standard

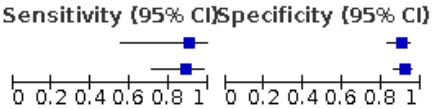
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Azevedo 2018	3	0	12	86	0.20 [0.04, 0.48]	1.00 [0.96, 1.00]
Bahr 2015	13	0	7	75	0.65 [0.41, 0.85]	1.00 [0.95, 1.00]
Bahr 2017	10	0	12	107	0.45 [0.24, 0.68]	1.00 [0.97, 1.00]
Cresswell 2020	25	0	20	159	0.56 [0.40, 0.70]	1.00 [0.98, 1.00]
Donovan 2020	21	0	22	59	0.49 [0.33, 0.65]	1.00 [0.94, 1.00]
Heemskerk 2018	95	0	284	231	0.25 [0.21, 0.30]	1.00 [0.98, 1.00]
Metcalf 2018	7	0	23	7	0.23 [0.10, 0.42]	1.00 [0.59, 1.00]
Nhu 2014	108	1	43	227	0.72 [0.64, 0.79]	1.00 [0.98, 1.00]
Patel 2013	20	5	23	101	0.47 [0.31, 0.62]	0.95 [0.89, 0.98]
Rakotoarivelo 2018	12	0	15	50	0.44 [0.25, 0.65]	1.00 [0.93, 1.00]
Sharma 2014	17	0	17	176	0.50 [0.32, 0.68]	1.00 [0.98, 1.00]
Vadwai 2011	1	0	4	14	0.20 [0.01, 0.72]	1.00 [0.77, 1.00]
Wang 2019	8	0	35	17	0.19 [0.08, 0.33]	1.00 [0.80, 1.00]
Zeka 2011	3	0	2	26	0.60 [0.15, 0.95]	1.00 [0.87, 1.00]



Test 5. Cerebrospinal fluid, Xpert Ultra, HIV positive

Cerebrospinal fluid, Xpert Ultra, HIV positive

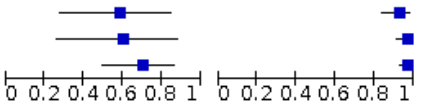
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bahr 2017	9	12	1	107	0.90 [0.55, 1.00]	0.90 [0.83, 0.95]
Cresswell 2020	24	15	3	162	0.89 [0.71, 0.98]	0.92 [0.86, 0.95]



Test 6. Cerebrospinal fluid, Xpert MTB/RIF, HIV positive

Cerebrospinal fluid, Xpert MTB/RIF, HIV positive

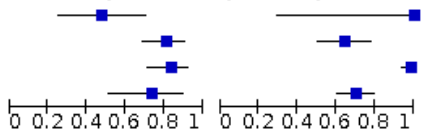
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bahr 2015	7	5	5	63	0.58 [0.28, 0.85]	0.93 [0.84, 0.98]
Bahr 2017	6	4	4	115	0.60 [0.26, 0.88]	0.97 [0.92, 0.99]
Cresswell 2020	19	6	8	171	0.70 [0.50, 0.86]	0.97 [0.93, 0.99]



Test 7. Pleural fluid, Xpert Ultra, culture

Pleural fluid, Xpert Ultra, culture

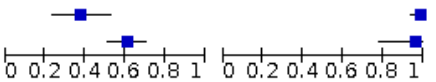
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perez-Risco 2018	10	0	11	3	0.48 [0.26, 0.70]	1.00 [0.29, 1.00]
Wang 2019	48	18	11	33	0.81 [0.69, 0.90]	0.65 [0.50, 0.78]
Wang 2020	46	1	9	83	0.84 [0.71, 0.92]	0.99 [0.94, 1.00]
Wu 2019	17	30	6	72	0.74 [0.52, 0.90]	0.71 [0.61, 0.79]



Test 8. Pleural fluid, Xpert Ultra, composite reference standard

Pleural fluid, Xpert Ultra, composite reference standard

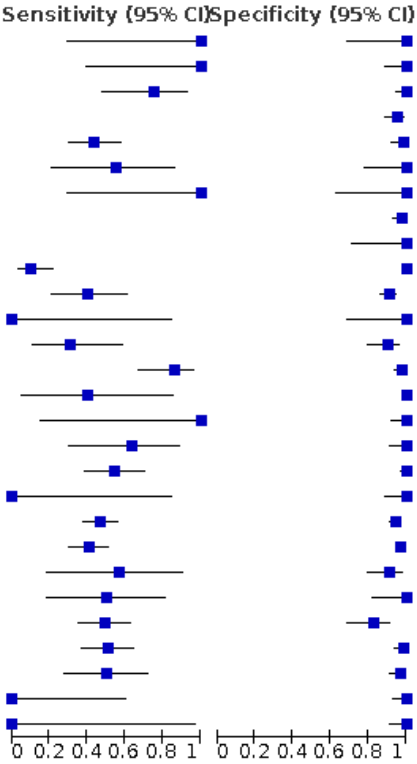
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Meldau 2019	18	1	30	83	0.38 [0.24, 0.53]	0.99 [0.94, 1.00]
Wang 2019	66	1	42	22	0.61 [0.51, 0.70]	0.96 [0.78, 1.00]



Test 9. Pleural fluid, Xpert MTB/RIF, culture

Pleural fluid, Xpert MTB/RIF, culture

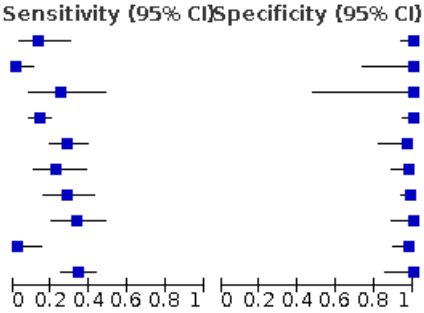
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	3	0	0	10	1.00 [0.29, 1.00]	1.00 [0.69, 1.00]
Causse 2011	4	0	0	30	1.00 [0.40, 1.00]	1.00 [0.88, 1.00]
Che 2017	12	0	4	62	0.75 [0.48, 0.93]	1.00 [0.94, 1.00]
Christopher 2013	0	4	0	83	Not estimable	0.95 [0.89, 0.99]
Du 2015	24	1	31	70	0.44 [0.30, 0.58]	0.99 [0.92, 1.00]
Friedrich 2011	5	0	4	15	0.56 [0.21, 0.86]	1.00 [0.78, 1.00]
Hanif 2011	3	0	0	8	1.00 [0.29, 1.00]	1.00 [0.63, 1.00]
Hillemann 2011	0	2	0	103	Not estimable	0.98 [0.93, 1.00]
Iram 2015	0	0	0	11	Not estimable	1.00 [0.72, 1.00]
Kim 2015a	5	0	44	339	0.10 [0.03, 0.22]	1.00 [0.99, 1.00]
Li 2017	10	18	15	178	0.40 [0.21, 0.61]	0.91 [0.86, 0.94]
Malbruny 2011	0	0	2	10	0.00 [0.00, 0.84]	1.00 [0.69, 1.00]
Meldau 2014	5	6	11	54	0.31 [0.11, 0.59]	0.90 [0.79, 0.96]
Nataraj 2016	24	3	4	136	0.86 [0.67, 0.96]	0.98 [0.94, 1.00]
Ozkutuk 2014	2	0	3	227	0.40 [0.05, 0.85]	1.00 [0.98, 1.00]
Peñata 2016	2	0	0	46	1.00 [0.16, 1.00]	1.00 [0.92, 1.00]
Rakotoarivelo 2018	7	0	4	39	0.64 [0.31, 0.89]	1.00 [0.91, 1.00]
Rufai 2015	23	0	19	119	0.55 [0.39, 0.70]	1.00 [0.97, 1.00]
Safianowska 2012	0	0	2	30	0.00 [0.00, 0.84]	1.00 [0.88, 1.00]
Scott 2014	59	21	66	336	0.47 [0.38, 0.56]	0.94 [0.91, 0.96]
Sharma 2014	37	8	54	265	0.41 [0.30, 0.51]	0.97 [0.94, 0.99]
Suzana 2016	4	4	3	42	0.57 [0.18, 0.90]	0.91 [0.79, 0.98]
Vadwai 2011	5	0	5	19	0.50 [0.19, 0.81]	1.00 [0.82, 1.00]
Wang 2019	28	9	29	42	0.49 [0.36, 0.63]	0.82 [0.69, 0.92]
Wang 2020	28	1	27	83	0.51 [0.37, 0.65]	0.99 [0.94, 1.00]
Wu 2019	11	3	11	94	0.50 [0.28, 0.72]	0.97 [0.91, 0.99]
Zeka 2011	0	0	4	52	0.00 [0.00, 0.60]	1.00 [0.93, 1.00]
Zmak 2013	0	0	1	41	0.00 [0.00, 0.97]	1.00 [0.91, 1.00]



Test 10. Pleural fluid, Xpert MTB/RIF, composite reference standard

Pleural fluid, Xpert MTB/RIF, composite reference standard

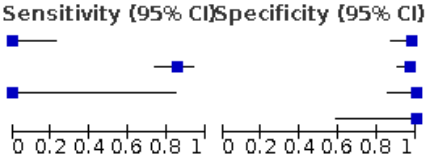
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christopher 2013	4	0	26	61	0.13 [0.04, 0.31]	1.00 [0.94, 1.00]
El-Din 2019	1	0	45	12	0.02 [0.00, 0.12]	1.00 [0.74, 1.00]
Friedrich 2011	5	0	15	5	0.25 [0.09, 0.49]	1.00 [0.48, 1.00]
Liang 2019	22	0	133	64	0.14 [0.09, 0.21]	1.00 [0.94, 1.00]
Lusiba 2014	25	1	62	28	0.29 [0.20, 0.39]	0.97 [0.82, 1.00]
Meldau 2014	9	1	31	47	0.23 [0.11, 0.38]	0.98 [0.89, 1.00]
Meldau 2019	14	1	35	83	0.29 [0.17, 0.43]	0.99 [0.94, 1.00]
Sharma 2018	16	0	32	30	0.33 [0.20, 0.48]	1.00 [0.88, 1.00]
Trajman 2014	1	1	32	51	0.03 [0.00, 0.16]	0.98 [0.90, 1.00]
Wu 2019	37	0	71	23	0.34 [0.25, 0.44]	1.00 [0.85, 1.00]



Test 11. Pleural tissue, Xpert MTB/RIF, culture

Pleural tissue, Xpert MTB/RIF, culture

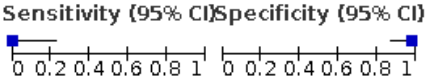
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christopher 2013	0	1	14	40	0.00 [0.00, 0.23]	0.98 [0.87, 1.00]
Du 2015	47	2	8	69	0.85 [0.73, 0.94]	0.97 [0.90, 1.00]
Ozkutuk 2014	0	0	2	24	0.00 [0.00, 0.84]	1.00 [0.86, 1.00]
Suzana 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]



Test 12. Pleural tissue, Xpert MTB/RIF, composite reference standard

Pleural tissue, Xpert MTB/RIF, composite reference standard

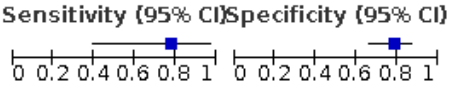
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Christopher 2013	0	1	14	40	0.00 [0.00, 0.23]	0.98 [0.87, 1.00]



Test 13. Lymph node aspirate, Xpert Ultra, culture

Lymph node aspirate, Xpert Ultra, culture

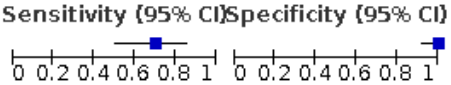
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	7	14	2	50	0.78 [0.40, 0.97]	0.78 [0.66, 0.87]



Test 14. Lymph node aspirate, Xpert Ultra, composite reference standard

Lymph node aspirate, Xpert Ultra, composite reference standard

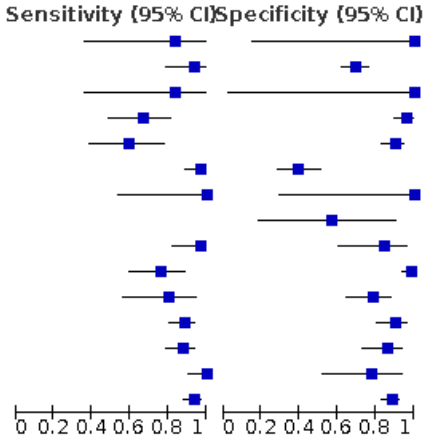
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	21	0	9	43	0.70 [0.51, 0.85]	1.00 [0.92, 1.00]



Test 15. Lymph node aspirate, Xpert MTB/RIF, culture

Lymph node aspirate, Xpert MTB/RIF, culture

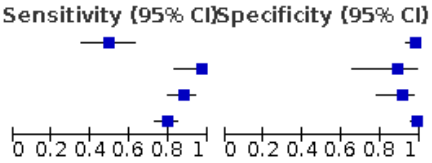
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	5	0	1	2	0.83 [0.36, 1.00]	1.00 [0.16, 1.00]
Biadglegne 2014	29	56	2	126	0.94 [0.79, 0.99]	0.69 [0.62, 0.76]
Blaich 2014	5	0	1	1	0.83 [0.36, 1.00]	1.00 [0.03, 1.00]
Dhasmana 2014	24	3	12	77	0.67 [0.49, 0.81]	0.96 [0.89, 0.99]
Dhooria 2016	16	12	11	108	0.59 [0.39, 0.78]	0.90 [0.83, 0.95]
Ghariani 2015	58	48	2	31	0.97 [0.88, 1.00]	0.39 [0.28, 0.51]
Hanif 2011	6	0	0	3	1.00 [0.54, 1.00]	1.00 [0.29, 1.00]
Kim 2015a	0	3	0	4	Not estimable	0.57 [0.18, 0.90]
Ligthelm 2011	28	3	1	16	0.97 [0.82, 1.00]	0.84 [0.60, 0.97]
Nataraj 2016	29	1	9	87	0.76 [0.60, 0.89]	0.99 [0.94, 1.00]
Scott 2014	16	12	4	43	0.80 [0.56, 0.94]	0.78 [0.65, 0.88]
Sharma 2014	85	7	11	63	0.89 [0.80, 0.94]	0.90 [0.80, 0.96]
Tadesse 2015	76	7	11	42	0.87 [0.79, 0.94]	0.86 [0.73, 0.94]
Ullah 2017	36	4	0	14	1.00 [0.90, 1.00]	0.78 [0.52, 0.94]
Van Rie 2013	139	23	10	172	0.93 [0.88, 0.97]	0.88 [0.83, 0.92]



Test 16. Lymph node aspirate, Xpert MTB/RIF, composite reference standard

Lymph node aspirate, Xpert MTB/RIF, composite reference standard

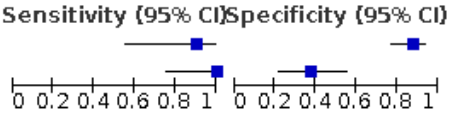
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Dhooria 2016	26	2	27	92	0.49 [0.35, 0.63]	0.98 [0.93, 1.00]
Ligthelm 2011	29	2	1	16	0.97 [0.83, 1.00]	0.89 [0.65, 0.99]
Tadesse 2015	81	4	11	40	0.88 [0.80, 0.94]	0.91 [0.78, 0.97]
Van Rie 2013	160	2	42	144	0.79 [0.73, 0.85]	0.99 [0.95, 1.00]



Test 17. Lymph node biopsy, Xpert Ultra, culture

Lymph node biopsy, Xpert Ultra, culture

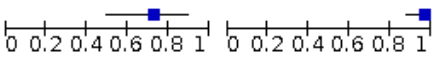
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	9	9	1	62	0.90 [0.55, 1.00]	0.87 [0.77, 0.94]
Wu 2019	13	23	0	14	1.00 [0.75, 1.00]	0.38 [0.22, 0.55]



Test 18. Lymph node biopsy, Xpert Ultra, composite reference standard

Lymph node biopsy, Xpert Ultra, composite reference standard

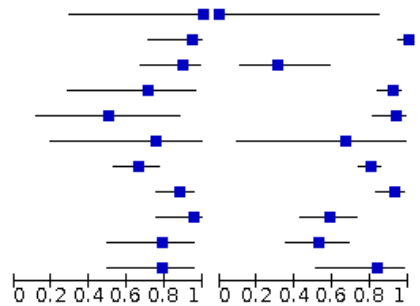
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Antel 2020	16	2	6	55	0.73 [0.50, 0.89]	0.96 [0.88, 1.00]



Test 19. Lymph node biopsy, Xpert MTB/RIF, culture

Lymph node biopsy, Xpert MTB/RIF, culture

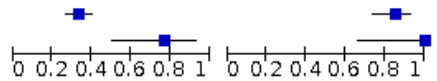
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blaich 2014	3	2	0	0	1.00 [0.29, 1.00]	0.00 [0.00, 0.84]
Causse 2011	16	0	1	70	0.94 [0.71, 1.00]	1.00 [0.95, 1.00]
Ghariani 2015	17	11	2	5	0.89 [0.67, 0.99]	0.31 [0.11, 0.59]
Kim 2015a	5	7	2	76	0.71 [0.29, 0.96]	0.92 [0.83, 0.97]
Ozkutuk 2014	3	3	3	41	0.50 [0.12, 0.88]	0.93 [0.81, 0.99]
Peñata 2016	3	1	1	2	0.75 [0.19, 0.99]	0.67 [0.09, 0.99]
Sarfaraz 2018	44	38	23	156	0.66 [0.53, 0.77]	0.80 [0.74, 0.86]
Sharma 2014	43	4	6	54	0.88 [0.75, 0.95]	0.93 [0.83, 0.98]
Suzana 2016	19	19	1	27	0.95 [0.75, 1.00]	0.59 [0.43, 0.73]
Wu 2019	11	18	3	20	0.79 [0.49, 0.95]	0.53 [0.36, 0.69]
Zeka 2011	11	2	3	10	0.79 [0.49, 0.95]	0.83 [0.52, 0.98]



Test 20. Lymph node biopsy, Xpert MTB/RIF, composite

Lymph node biopsy, Xpert MTB/RIF, composite

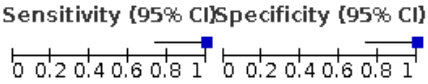
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sarfaraz 2018	67	9	135	51	0.33 [0.27, 0.40]	0.85 [0.73, 0.93]
Zeka 2011	13	0	4	9	0.76 [0.50, 0.93]	1.00 [0.66, 1.00]



Test 21. Urine, Xpert Ultra, culture

Urine, Xpert Ultra, culture

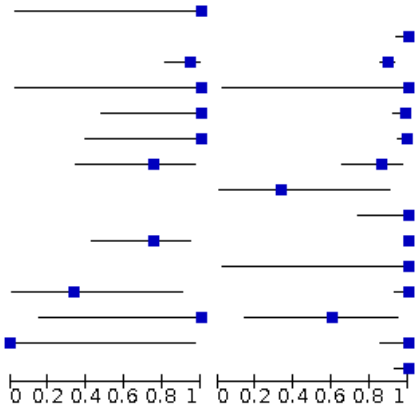
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perez-Risco 2018	12	0	0	12	1.00 [0.74, 1.00]	1.00 [0.74, 1.00]



Test 22. Urine, Xpert MTB/RIF, culture

Urine, Xpert MTB/RIF, culture

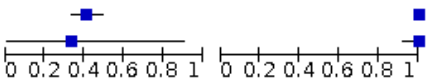
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Blaich 2014	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Causse 2011	0	0	0	58	Not estimable	1.00 [0.94, 1.00]
Chen 2019	34	28	2	238	0.94 [0.81, 0.99]	0.89 [0.85, 0.93]
Hanif 2011	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Hillemann 2011	5	1	0	70	1.00 [0.48, 1.00]	0.99 [0.92, 1.00]
Kim 2015a	4	1	0	101	1.00 [0.40, 1.00]	0.99 [0.95, 1.00]
Li 2017	6	3	2	19	0.75 [0.35, 0.97]	0.86 [0.65, 0.97]
Malbruny 2011	0	2	0	1	Not estimable	0.33 [0.01, 0.91]
Nataraj 2016	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Ozkutuk 2014	9	0	3	329	0.75 [0.43, 0.95]	1.00 [0.99, 1.00]
Safianowska 2012	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Sharma 2014	1	0	2	52	0.33 [0.01, 0.91]	1.00 [0.93, 1.00]
Suzana 2016	2	2	0	3	1.00 [0.16, 1.00]	0.60 [0.15, 0.95]
Zeka 2011	0	0	1	23	0.00 [0.00, 0.97]	1.00 [0.85, 1.00]
Zmak 2013	0	0	0	50	Not estimable	1.00 [0.93, 1.00]



Test 23. Urine, Xpert MTB/RIF, composite reference standard

Urine, Xpert MTB/RIF, composite reference standard

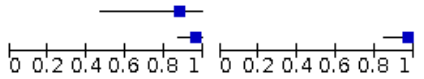
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2019	62	0	88	266	0.41 [0.33, 0.50]	1.00 [0.99, 1.00]
Sharma 2014	1	0	2	44	0.33 [0.01, 0.91]	1.00 [0.92, 1.00]



Test 24. Bone or joint aspirate, Xpert Ultra, culture

Bone or joint aspirate, Xpert Ultra, culture

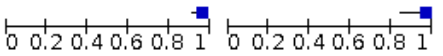
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perez-Risco 2018	7	0	1	0	0.88 [0.47, 1.00]	Not estimable
Sun 2019	50	1	2	33	0.96 [0.87, 1.00]	0.97 [0.85, 1.00]



Test 25. Bone or joint aspirate, Xpert Ultra, composite reference standard

Bone or joint aspirate, Xpert Ultra, composite reference standard

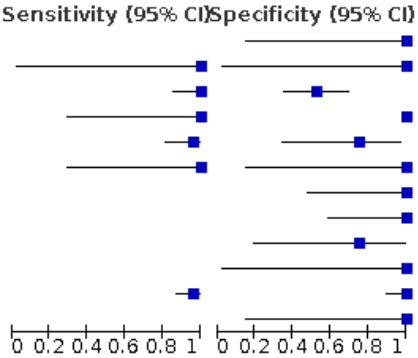
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Sun 2019	107	1	4	33	0.96 [0.91, 0.99]	0.97 [0.85, 1.00]



Test 26. Bone or joint aspirate, Xpert MTB/RIF, culture

Bone or joint aspirate, Xpert MTB/RIF, culture

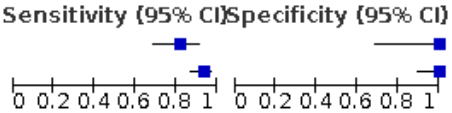
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	2	Not estimable	1.00 [0.16, 1.00]
Blaich 2014	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Gu 2015	24	17	0	19	1.00 [0.86, 1.00]	0.53 [0.35, 0.70]
Kim 2015a	3	0	0	280	1.00 [0.29, 1.00]	1.00 [0.99, 1.00]
Li 2017	26	2	1	6	0.96 [0.81, 1.00]	0.75 [0.35, 0.97]
Malbruny 2011	3	0	0	2	1.00 [0.29, 1.00]	1.00 [0.16, 1.00]
Nataraj 2016	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Ozkutuk 2014	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Peñata 2016	0	1	0	3	Not estimable	0.75 [0.19, 0.99]
Safianowska 2012	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Sun 2019	50	0	2	34	0.96 [0.87, 1.00]	1.00 [0.90, 1.00]
Suzana 2016	0	0	0	2	Not estimable	1.00 [0.16, 1.00]



Test 27. Bone or Joint aspirate, Xpert MTB/RIF, composite reference standard

Bone or Joint aspirate, Xpert MTB/RIF, composite reference standard

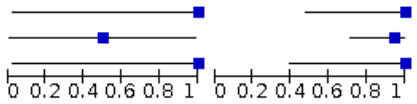
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Gu 2015	41	0	9	10	0.82 [0.69, 0.91]	1.00 [0.69, 1.00]
Sun 2019	104	0	7	34	0.94 [0.87, 0.97]	1.00 [0.90, 1.00]



Test 28. Bone or joint tissue, Xpert MTB/RIF, culture

Bone or joint tissue, Xpert MTB/RIF, culture

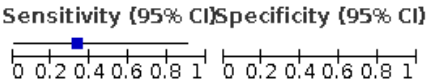
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Malbruny 2011	1	0	0	5	1.00 [0.03, 1.00]	1.00 [0.48, 1.00]
Ozkutuk 2014	1	1	1	16	0.50 [0.01, 0.99]	0.94 [0.71, 1.00]
Peñata 2016	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]



Test 29. Peritoneal fluid, Xpert Ultra, culture

Peritoneal fluid, Xpert Ultra, culture

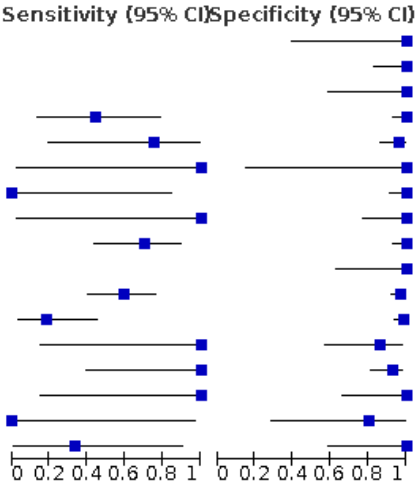
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Perez-Risco 2018	1	0	2	0	0.33 [0.01, 0.91]	Not estimable



Test 30. Peritoneal fluid, Xpert MTB/RIF, culture

Peritoneal fluid, Xpert MTB/RIF, culture

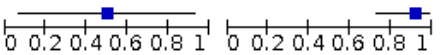
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Causse 2011	0	0	0	20	Not estimable	1.00 [0.83, 1.00]
Iram 2015	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Kim 2015a	4	0	5	50	0.44 [0.14, 0.79]	1.00 [0.93, 1.00]
Li 2017	3	2	1	48	0.75 [0.19, 0.99]	0.96 [0.86, 1.00]
Malbruny 2011	1	0	0	2	1.00 [0.03, 1.00]	1.00 [0.16, 1.00]
Ozkutuk 2014	0	0	2	40	0.00 [0.00, 0.84]	1.00 [0.91, 1.00]
Peñata 2016	1	0	0	14	1.00 [0.03, 1.00]	1.00 [0.77, 1.00]
Rufai 2017a	12	0	5	50	0.71 [0.44, 0.90]	1.00 [0.93, 1.00]
Safianowska 2012	0	0	0	8	Not estimable	1.00 [0.63, 1.00]
Scott 2014	19	3	13	104	0.59 [0.41, 0.76]	0.97 [0.92, 0.99]
Sharma 2014	3	1	13	85	0.19 [0.04, 0.46]	0.99 [0.94, 1.00]
Suzana 2016	2	2	0	12	1.00 [0.16, 1.00]	0.86 [0.57, 0.98]
Ullah 2017	4	4	0	48	1.00 [0.40, 1.00]	0.92 [0.81, 0.98]
Vadwai 2011	2	0	0	9	1.00 [0.16, 1.00]	1.00 [0.66, 1.00]
Zeka 2011	0	1	1	4	0.00 [0.00, 0.97]	0.80 [0.28, 0.99]
Zmak 2013	1	0	2	7	0.33 [0.01, 0.91]	1.00 [0.59, 1.00]



Test 31. Peritoneal tissue, Xpert MTB/RIF, culture

Peritoneal tissue, Xpert MTB/RIF, culture

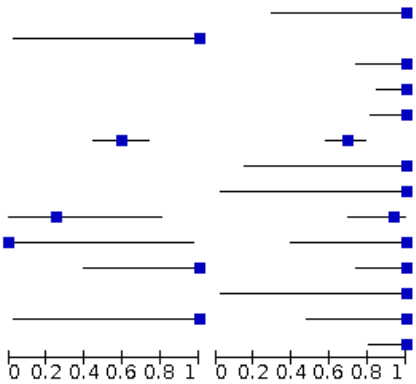
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Bera 2015	2	2	2	22	0.50 [0.07, 0.93]	0.92 [0.73, 0.99]



Test 32. Pericardial fluid, Xpert MTB/RIF, culture

Pericardial fluid, Xpert MTB/RIF, culture

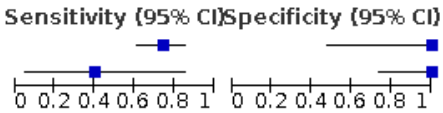
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Al-Ateah 2012	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Blaich 2014	1	0	0	0	1.00 [0.03, 1.00]	Not estimable
Causse 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Kim 2015a	0	0	0	22	Not estimable	1.00 [0.85, 1.00]
Ozkutuk 2014	0	0	0	18	Not estimable	1.00 [0.81, 1.00]
Pandie 2014	28	27	19	60	0.60 [0.44, 0.74]	0.69 [0.58, 0.78]
Peñata 2016	0	0	0	2	Not estimable	1.00 [0.16, 1.00]
Safianowska 2012	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Sharma 2014	1	1	3	15	0.25 [0.01, 0.81]	0.94 [0.70, 1.00]
Suzana 2016	0	0	1	4	0.00 [0.00, 0.97]	1.00 [0.40, 1.00]
Ullah 2017	4	0	0	12	1.00 [0.40, 1.00]	1.00 [0.74, 1.00]
Vadwai 2011	0	0	0	1	Not estimable	1.00 [0.03, 1.00]
Zeka 2011	1	0	0	5	1.00 [0.03, 1.00]	1.00 [0.48, 1.00]
Zmak 2013	0	0	0	17	Not estimable	1.00 [0.80, 1.00]



Test 33. Pericardial fluid, Xpert MTB/RIF, composite reference standard

Pericardial fluid, Xpert MTB/RIF, composite reference standard

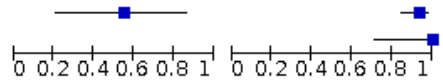
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Pandie 2014	41	0	14	5	0.75 [0.61, 0.85]	1.00 [0.48, 1.00]
Sharma 2014	2	0	3	12	0.40 [0.05, 0.85]	1.00 [0.74, 1.00]



Test 34. Blood, Xpert MTB/RIF, culture

Blood, Xpert MTB/RIF, culture

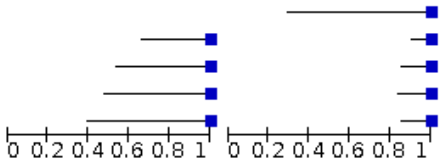
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Feasey 2013	5	4	4	61	0.56 [0.21, 0.86]	0.94 [0.85, 0.98]
Zmak 2013	0	0	0	11	Not estimable	1.00 [0.72, 1.00]



Test 35. Rifampicin resistance, Xpert Ultra

Rifampicin resistance, Xpert Ultra

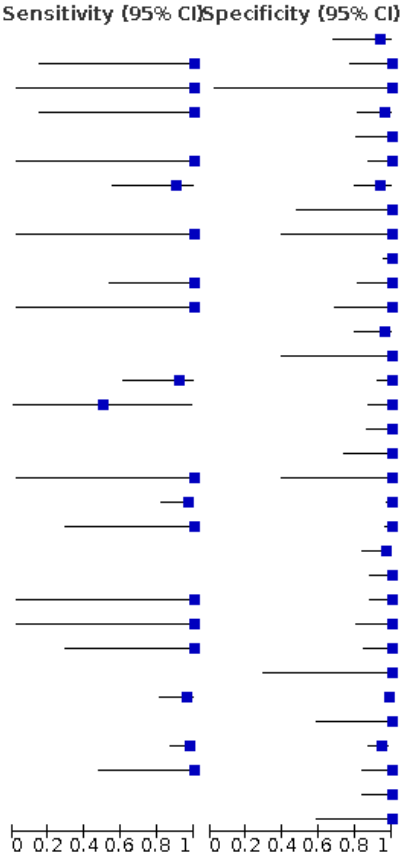
Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chin 2019	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Sun 2019	9	0	0	38	1.00 [0.66, 1.00]	1.00 [0.91, 1.00]
Wang 2019	6	0	0	23	1.00 [0.54, 1.00]	1.00 [0.85, 1.00]
Wang 2020	5	0	0	21	1.00 [0.48, 1.00]	1.00 [0.84, 1.00]
Wu 2019	4	0	0	23	1.00 [0.40, 1.00]	1.00 [0.85, 1.00]



Test 36. Rifampicin resistance, Xpert MTB/RIF

Rifampicin resistance, Xpert MTB/RIF

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ablanedo-Terrazas 2014	0	1	0	14	Not estimable	0.93 [0.68, 1.00]
Al-Ateah 2012	2	0	0	14	1.00 [0.16, 1.00]	1.00 [0.77, 1.00]
Bera 2015	1	0	0	1	1.00 [0.03, 1.00]	1.00 [0.03, 1.00]
Biadglegne 2014	2	1	0	26	1.00 [0.16, 1.00]	0.96 [0.81, 1.00]
Blaich 2014	0	0	0	17	Not estimable	1.00 [0.80, 1.00]
Dhasmana 2014	1	0	0	26	1.00 [0.03, 1.00]	1.00 [0.87, 1.00]
Du 2015	9	2	1	31	0.90 [0.55, 1.00]	0.94 [0.80, 0.99]
Feasey 2013	0	0	0	5	Not estimable	1.00 [0.48, 1.00]
Friedrich 2011	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Ghariani 2015	0	0	0	75	Not estimable	1.00 [0.95, 1.00]
Gu 2015	6	0	0	18	1.00 [0.54, 1.00]	1.00 [0.81, 1.00]
Hanif 2011	1	0	0	10	1.00 [0.03, 1.00]	1.00 [0.69, 1.00]
Hillemann 2011	0	1	0	24	Not estimable	0.96 [0.80, 1.00]
Iram 2015	0	0	0	4	Not estimable	1.00 [0.40, 1.00]
Li 2017	11	0	1	47	0.92 [0.62, 1.00]	1.00 [0.92, 1.00]
Ligthelm 2011	1	0	1	26	0.50 [0.01, 0.99]	1.00 [0.87, 1.00]
Lusiba 2014	0	0	0	25	Not estimable	1.00 [0.86, 1.00]
Malbruny 2011	0	0	0	12	Not estimable	1.00 [0.74, 1.00]
Meldau 2014	1	0	0	4	1.00 [0.03, 1.00]	1.00 [0.40, 1.00]
Nataraj 2016	28	0	1	121	0.97 [0.82, 1.00]	1.00 [0.97, 1.00]
Nhu 2014	3	0	0	104	1.00 [0.29, 1.00]	1.00 [0.97, 1.00]
Ozkutuk 2014	0	1	0	31	Not estimable	0.97 [0.84, 1.00]
Pandie 2014	0	0	0	28	Not estimable	1.00 [0.88, 1.00]
Peñata 2016	1	0	0	28	1.00 [0.03, 1.00]	1.00 [0.88, 1.00]
Rufai 2015	1	0	0	17	1.00 [0.03, 1.00]	1.00 [0.80, 1.00]
Rufai 2017b	3	0	0	22	1.00 [0.29, 1.00]	1.00 [0.85, 1.00]
Safianowska 2012	0	0	0	3	Not estimable	1.00 [0.29, 1.00]
Sharma 2014	26	3	1	211	0.96 [0.81, 1.00]	0.99 [0.96, 1.00]
Sharma 2016	0	0	0	7	Not estimable	1.00 [0.59, 1.00]
Vadwai 2011	39	5	1	80	0.97 [0.87, 1.00]	0.94 [0.87, 0.98]
Wang 2020	5	0	0	21	1.00 [0.48, 1.00]	1.00 [0.84, 1.00]
Zeka 2011	0	0	0	21	Not estimable	1.00 [0.84, 1.00]
Zmak 2013	0	0	0	7	Not estimable	1.00 [0.59, 1.00]



ADDITIONAL TABLES

Table 1. Forms of extrapulmonary TB

Form of extrapulmonary TB	Characteristics	Diagnostic specimens and means of collection
Tuberculous meningitis	Tuberculosis of the meninges affects people of all ages but is most common among children and people with untreated HIV infection. In adults, tuberculous meningitis presents with gradual onset of headache, neck stiffness, malaise, and fever, and if untreated can progress to altered sensorium, focal neurological deficits, coma, and death. Young children may present with poor weight gain, low-grade fever, and listlessness. Infants may present with fever, cough (related to the primary pulmonary infection that occurs before tuberculous meningitis develops), change of consciousness at presentation, bulging anterior fontanel, and seizures (Thwaites 2013). Tuberculous meningitis is sometimes associated with a concurrent cerebral tuberculoma, or, more rarely, a tuberculous abscess	Cerebrospinal fluid, acquired by lumbar puncture with or without radiological guidance; biopsy of tuberculoma, acquired surgically
Pleural tuberculosis, also called TB pleurisy	TB infection of the pleura presents with gradual onset of pleuritic chest pain, shortness of breath, fever, night sweats, and weight loss. Chest X-ray may demonstrate unilateral or occasionally bilateral pleural effusion. The severity of symptoms is highly variable, with many patients experiencing spontaneous resolution of symptoms, while others may develop severe pleural effusions requiring drainage. Pleuro-pulmonary tuberculosis, in which parenchymal lung involvement is visible on a	Pleural fluid; pleural biopsy, which may be performed via thoracoscopy or percutaneously with Abram's needle, with

Table 1. Forms of extrapulmonary TB *(Continued)*

	chest X-ray, is associated with higher mortality than isolated pleural infection, which appears to be rarely fatal (Shu 2011)	or without ultrasound guidance
Lymph node tuberculosis, also called TB lymphadenitis	Tuberculosis of the lymph nodes may affect one node or a group of nodes, or multiple groups within a chain. Lymph node tuberculosis is relatively more common among children than adults. The most common presentation is of a single, firm, non-tender enlarged node in the neck, although any lymph node group can be affected. This may be accompanied by fever, weight loss, and night sweats, particularly in people with HIV. Patients with tuberculosis in deep lymph nodes, such as the mediastinal or mesenteric lymph nodes, may present with fever, night sweats, and weight loss, or, more rarely, with symptoms related to compression of adjacent structures. Over time lymph nodes become fluctuant and may discharge via a sinus to the skin or an adjacent viscus. It should be noted that lymphadenopathy may also be seen in other forms of tuberculosis as part of the immune response, but this is not usually caused by direct infection of the lymph nodes	Fine-needle aspiration of fluid from affected lymph node, with or without radiological guidance; surgical biopsy of superficial lymph nodes; endoscopic biopsy of deep lymph nodes with ultrasound guidance
Bone or joint tuberculosis	Tuberculosis of bones or joints or both causes chronic pain, deformity, and disability, and tuberculosis of the cervical spine can be life-threatening. The usual presenting symptom is pain. Fever and weight loss, with or without signs of spinal cord compression, may be present. Patients with advanced disease may have severe pain, spinal deformity, paraspinal muscle wasting, and neurological deficit. Children may have failure to thrive and difficulty walking	Aspiration of joint fluid or periarticular abscesses; percutaneous computed tomography-guided biopsy of lesions is preferred, but some patients may require open biopsy
Genitourinary tuberculosis	Tuberculosis of the genitourinary tract includes renal tuberculosis and tuberculosis of the reproductive system. Renal tuberculosis presents with flank pain, haematuria, and dysuria. Female genital tuberculosis presents with infertility (and may be otherwise asymptomatic), pelvic pain, and vaginal bleeding. Testicular tuberculosis presents with a scrotal mass and infertility	Urine; biopsy of affected organs, acquired under radiological guidance or surgically
Pericardial tuberculosis, also called TB pericarditis	Tuberculosis of the pericardium presents with fever, malaise, night sweats, and weight loss. Chest pain and shortness of breath are also commonly-experienced symptoms. Pericardial tuberculosis may be associated with pericardial effusion, which can be severe and lead to life-threatening tamponade. Some patients go on to develop pericardial constriction, which can lead to heart failure and death and may require surgical intervention even after mycobacterial cure	Pericardial fluid acquired by pericardiocentesis; pericardial biopsy, acquired under radiological guidance or surgically
Peritoneal tuberculosis	Tuberculosis of the peritoneum usually presents with pain and abdominal swelling, which may be accompanied by fever, weight loss, and anorexia	Ascitic fluid acquired by paracentesis; peritoneal biopsy (Chow 2002)
Disseminated tuberculosis, also called miliary tuberculosis. It has been proposed that the designation 'miliary TB' be restricted to disseminated TB with miliary shadows on chest radiograph (Reuter 2009)	Disseminated tuberculosis involves two or more distinctly separate sites. Manifestations may be varied, ranging from acute fulminant disease to non-specific symptoms of fever, weight loss, and weakness. HIV-positive people are more likely to have disseminated tuberculosis than HIV-negative people. In a systematic review of the prevalence of tuberculosis in post mortem evaluations of HIV-positive people, among adults disseminated tuberculosis was found in 88% of tuberculosis cases and was considered the cause of death in 91% of TB cases (Gupta 2015)	Blood; specimens acquired from affected extrapulmonary sites

Abbreviations: TB: tuberculosis.
We adapted the table from Sharma 2017b.

Table 2. Summary accuracy of Xpert MTB/RIF and Xpert Ultra for detection of extrapulmonary tuberculosis and rifampicin resistance

Type of specimen	Test	Reference standard	Number studies (participants)	Number (%) with TB or rifampicin resistance	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)	Positive predictive value (95% CrI)	Negative predictive value (95% CrI)
CSF	Xpert Ultra	culture	6 (475)	89 (18.7)	89.4% (79.1 to 95.6)	91.2% (83.2 to 95.7)	53.0% (36.6 to 69.6)	98.7% (97.5 to 99.5)
CSF	Xpert Ultra	composite	4 (496)	160 (32.2)	62.7% (45.7 to 77.0)	99.1% (96.6 to 99.9)	87.9% (65.5 to 99.0)	96.0% (94.2 to 97.5)
CSF	Xpert MTB/RIF	culture	30 (3395)	571 (16.8)	71.1% (62.8 to 79.1)	96.9% (95.4 to 98.0)	71.8% (62.3 to 80.7)	96.8% (95.9 to 97.7)
CSF	Xpert MTB/RIF	composite	14 (2203)	862 (39.1)	42.3% (32.1 to 52.8)	99.8% (99.3 to 100.0)	96.3% (87.2 to 100.0)	94.0% (93.0 to 95.0)
CSF	Ultra, direct comparison	culture	5 (471)	86 (18.3)	89.0% (77.9 to 95.2)	91.0% (82.7 to 95.6)	52.2% (35.6 to 69.0)	98.7% (97.3 to 99.4)
CSF	Xpert MTB/RIF, direct comparison	culture	5 (471)	87 (18.5)	62.2% (43.7 to 78.1)	96.8% (93.4 to 98.6)	68.4% (49.0 to 83.6)	95.8% (93.9 to 97.5)
Pleural fluid	Xpert Ultra	culture	4 (398)	158 (39.7)	75.0% (58.0 to 86.4)	87.0% (63.1 to 97.9)	38.8% (17.9 to 79.5)	96.9% (94.5 to 98.3)
Pleural fluid	Xpert MTB/RIF	culture	25 (3065)	644 (21.0)	49.5% (39.8 to 59.9)	98.9% (97.6 to 99.7)	83.2% (68.9 to 94.6)	94.6% (93.7 to 95.7)
Pleural fluid	Xpert MTB/RIF	composite	10 (1024)	616 (60.1)	18.9% (11.5 to 27.9)	99.3% (98.1 to 99.8)	73.6% (49.2 to 91.2)	91.7% (91.0 to 92.5)
Lymph node aspirate	Xpert MTB/RIF	culture	14 (1588)	627 (39.5)	88.9% (82.7 to 93.6)	86.2% (78.0 to 92.3)	41.7% (31.4 to 55.5)	98.6% (97.9 to 99.2)
Lymph node aspirate	Xpert MTB/RIF	composite	4 (679)	377 (55.5)	81.6% (61.9 to 93.3)	96.4% (91.3 to 98.6)	71.0% (51.1 to 86.1)	97.9% (95.8 to 99.2)

Table 2. Summary accuracy of Xpert MTB/RIF and Xpert Ultra for detection of extrapulmonary tuberculosis and rifampicin resistance *(Continued)*

Lymph node biopsy	Xpert MTB/RIF	culture	11 (786)	220 (28.0)	82.4% (73.5 to 89.7)	80.3% (60.3 to 91.5)	31.6% (18.7 to 51.8)	97.6% (96.2 to 98.6)
Urine	Xpert MTB/RIF	culture	9 (943)	72 (7.6)	85.9% (71.4 to 94.3)	98.1% (93.1 to 99.7)	83.0% (58.3 to 96.7)	98.4% (96.9 to 99.4)
Bone or joint aspirate	Xpert MTB/RIF	culture	6 (471)	110 (23.4)	97.9% (93.1 to 99.6)	97.4% (80.2 to 100.0)	80.7% (35.4 to 99.5)	99.8% (99.2 to 100.0)
Peritoneal fluid	Xpert MTB/RIF	culture	13 (580)	94 (16.2)	59.1% (42.1 to 76.2)	97.6% (95.4 to 98.9)	73.0% (58.2 to 86.2)	95.5% (93.8 to 97.4)
Pericardial fluid	Xpert MTB/RIF	culture	5 (181)	57 (31.5)	61.4% (32.4 to 82.4)	89.7% (74.9 to 99.0)	39.4% (18.3 to 88.0)	95.4% (92.1 to 97.9)
Rifampicin resistance	Xpert Ultra	DSTor LPA	4 (129)	24 (18.6)	100.0% (95.1 to 100.0)	100.0% (99.0 to 100.0)	99.9% (91.7 to 100.0)	100.0% (99.5 to 100.0)
Rifampicin resistance	Xpert MTB/RIF	DSTor LPA	19 (970)	148 (15.3)	96.5% (91.9 to 98.8)	99.1% (98.0 to 99.7)	92.0% (84.3 to 97.3)	99.6% (99.1 to 99.9)

Abbreviations: CrI: credible interval; CSF: cerebrospinal fluid; LPA: Line probe assay; TB: tuberculosis.
Studies included in the table are limited to those that report data for both sensitivity and specificity; thus the number of studies (specimens) may differ slightly from those reported in the main text of the review. For tuberculosis detection, the reference standard was culture and a composite reference standard. For rifampicin resistance detection, the reference standards were culture-based drug susceptibility testing or line probe assay. Pooled sensitivity and pooled specificity are posterior median estimates.

Table 3. Latent class meta-analysis

Form of extrapulmonary tuberculosis, type of specimen	Number of studies (participants)	Culture-confirmed tuberculosis (%)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)	Positive predictive value (95% CrI)	Negative predictive value (95% CrI)
Accuracy estimates of Xpert MTB/RIF						
Tuberculous meningitis, cerebrospinal fluid	30 (3395)	571 (16.8)	74.7% (65.5 to 84.0)	99.5% (99.1 to 99.7)	94.5% (89.7 to 96.9)	97.3% (96.3 to 98.3)
Pleural tuberculosis, fluid	25 (3065)	644 (21.0)	53.1% (42.8 to 64.1)	99.6% (99.3 to 99.8)	93.7% (89.5 to 96.5)	95.0% (94.0 to 96.2)
Lymph node tuberculosis, aspirate	14 (1588)	627 (39.5)	91.5% (85.2 to 95.9)	99.5% (99.1 to 99.7)	95.2% (91.4 to 97.5)	99.1% (98.4 to 99.5)
Accuracy estimates of culture						
Tuberculous meningitis, cerebrospinal fluid	30 (3395)	571 (16.8)	80.8% (72.5 to 88.5)	99.2% (98.7 to 99.5)	91.9% (86.9 to 95.1)	97.9% (97.0 to 98.7)
Pleural tuberculosis, fluid	25 (3065)	644 (21.0)	89.5% (80.5 to 96.3)	99.0% (98.2 to 99.5)	90.8% (84.2 to 94.7)	98.8% (97.9 to 99.6)
Lymph node tuberculosis, aspirate	14 (1588)	627 (39.5)	82.9% (69.9 to 91.8)	98.8% (97.8 to 99.4)	88.7% (80.1 to 94.0)	98.1% (96.7 to 99.1)

Abbreviations: CrI: credible interval.
We generally used non-informative priors in the latent class model.
Accuracy estimates were determined using a bivariate random-effects approach for comparison.

Table 4. Accuracy of Xpert Ultra versus Xpert MTB/RIF in cerebrospinal fluid

Detection of tuberculosis in CSF				
Test (studies, participants)	**Xpert Ultra (5, 471)**	**Xpert MTB/RIF (5, 471)**	**Difference (Xpert Ultra minus Xpert MTB/RIF)**	**Probability (Xpert Ultra minus Xpert MTB/RIF)**
Sensitivity	89.0% (77.9 to 95.2)	62.2% (43.7 to 78.1)	26.2% (9.1 to 44.4)	0.997
Specificity	91.0% (82.7 to 95.6)	96.8% (93.4 to 98.6)	−5.6% (−12.9 to −0.1)	0.022

Table 5. Impact of concentrating cerebrospinal fluid on Xpert Ultra and Xpert MTB/RIF sensitivity and specificity

Covariate (number of studies, participants)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
Concentration step, Xpert Ultra		

Table 5. Impact of concentrating cerebrospinal fluid on Xpert Ultra and Xpert MTB/RIF sensitivity and specificity *(Continued)*

Concentrated specimen (3, 421)	90.5% (76.7 to 97.0)	91.9% (84.5 to 96.1)
Unconcentrated specimen (3, 54)	88.4% (67.8 to 97.5)	88.6% (58.4 to 99.0)
Difference (concentrated minus unconcentrated)	2.6% (−13.9 to 24.1)	3.4% (−9.5 to 32.8)
Probability (concentrated minus unconcentrated)	0.630	0.653
Concentration step, Xpert MTB/RIF		
Concentrated specimen (14, 2279)	77.6% (67.2 to 85.9)	97.4% (96.1 to 98.4)
Unconcentrated specimen (17, 1123)	59.4% (48.3 to 70.5)	96.8% (94.0 to 98.7)
Difference (concentrated minus unconcentrated)	18.4% (2.8 to 32.1)	0.6% (−1.7 to 3.6)
Probability (concentrated minus unconcentrated)	0.989	0.696

Abbreviations: CrI: credible interval.

Table 6. Impact of tuberculosis prevalence on Xpert Ultra and Xpert MTB/RIF sensitivity and specificity

Analysis, (number of studies, specimens)	Pooled sensitivity (95% CrI)	Pooled specificity (95% CrI)
Cerebrospinal fluid, Xpert Ultra		
Among studies with prevalence ≥ 30% (3, 54)	88.3% (68.3 to 97.0)	88.0% (64.3 to 97.9)
Among studies with prevalence < 30% (3, 421)	90.8% (77.3 to 96.9)	91.9% (82.5 to 96.6)
Difference (≥ 30% group minus < 30% group)	−2.2% (−23.0 to 13.5)	−3.8% (−27.7 to 9.8)
Probability (≥ 30% group minus < 30% group)	0.390	0.308
Cerebrospinal fluid, Xpert MTB/RIF		
Among studies with prevalence ≥ 30% (6, 610)	67.0% (49.0 to 81.5)	94.1% (86.8 to 97.9)
Among studies with prevalence < 30% (24, 2785)	72.0% (62.4 to 81.2)	97.3% (95.9 to 98.3)
Difference (≥ 30% group minus < 30% group)	−4.8% (−25.5 to 12.1)	−3.1% (−10.5 to 0.8)
Probability (≥ 30% group minus < 30% group)	0.296	0.071
Cerebrospinal fluid, Xpert MTB/RIF		
Among studies with prevalence ≥ 10% (19, 2190)	68.7% (58.5 to 78.0)	95.1% (92.7 to 96.8)
Among studies with prevalence < 10% (11, 1205)	74.2% (57.4 to 86.6)	98.6% (97.5 to 99.3)
Difference (≥ 10% group minus < 10% group)	-5.5% (-21.2 to 13.3)	-3.5% (-6.0 to -1.5)
Probability (≥ 10% group minus < 10% group)	0.272	0.001

Table 6. Impact of tuberculosis prevalence on Xpert Ultra and Xpert MTB/RIF sensitivity and specificity *(Continued)*

Pleural fluid, Xpert MTB/RIF		
Among studies with prevalence ≥ 50% (6, 627)	20.7% (11.2 to 33.7)	99.6% (97.9 to 99.9)
Among studies with prevalence < 50% (4, 397)	15.5% (6.5 to 30.1)	99.0% (96.9 to 99.8)
Difference (≥ 50% group minus < 50% group)	5.1% (−11.8 to 21.2)	0.5% (−1.2 to 2.7)
Probability (≥ 50% group minus < 50% group)	0.757	0.759
Lymph node aspirate, Xpert MTB/RIF		
Among studies with prevalence ≥ 35 (9, 911)	93.1% (88.9 to 96.3)	83.2% (69.5 to 92.1)
Among studies with prevalence < 35% (5, 677)	72.2% (64.9 to 87.2)	90.0% (78.3 to 95.9)
Difference (≥ 35% group minus < 35% group)	15.7% (5.4 to 28.6)	−6.4% (−21.3 to 76)
Probability (≥ 35% group minus < 35% group)	0.999	0.158

Abbreviations: Crl: credible interval.
Prevalence refers to the percentage of culture-confirmed tuberculosis specimens or confirmed rifampicin-resistant specimens in the study. We selected prevalence levels to approximate the lower bound of the interquartile range or in consideration of the range of prevalences reported in the included studies.

Table 7. Sensitivity analyses, Xpert Ultra in cerebrospinal fluid

Type of specimen	Number of studies (specimens)	Pooled sensitivity (95% Crl)	Pooled specificity (95% Crl)	Predicted sensitivity (95% Crl)	Predicted specificity (95% Crl)
All participants	6 (475)	89.4% (79.1 to 95.6)	91.2% (83.2 to 95.7)	53.0% (36.6 to 69.6)	98.7% (97.5 to 99.5)
Consecutive participant selection	5 (471)	87.9% (76.4 to 94.6)	90.4% (81.1 to 95.1)	88.0% (65.2 to 96.7)	90.5% (65.5 to 97.7)
Reference standard blinding	4 (432)	88.5% (74.7 to 95.6)	89.1% (76.9 to 94.3)	88.6% (63.4 to 97.2)	89.2% (61.0 to 97.1)
Single specimen per participant	4 (432)	88.5% (74.7 to 95.6)	89.1% (76.9 to 94.3)	88.6% (63.4 to 97.2)	89.2% (61.0 to 97.1)

Abbreviations: Crl: credible interval.

Table 8. Systematic reviews of Xpert MTB/RIF and Xpert Ultra for extrapulmonary tuberculosis

Systematic review	Search period	Index test	Number of studies (total number of extrapulmonary specimens)	Forms of extrapulmonary TB or types of specimens	Accuracy against culture reference standard		
					Tuberculous meningitis	Pleural tuberculosis (pleural fluid)	Lymph node tuberculosis
Chang 2012 [a]	Up to 1 October 2011	Xpert MTB/RIF	7 (1058)	Multiple forms combined	Not reported	Not reported	Not reported
Denkinger 2014 [b]	Up to 15 October 2013	Xpert MTB/RIF	18 (4461)	Lymph node, pleural fluid, CSF	Sensitivity 81%; specificity 98%	Sensitivity 46%; specificity 99%	Sensitivity 83%; specificity 94%
Maynard-Smith 2014	Up to 6 November 2013	Xpert MTB/RIF	27 (6026)	Lymph node, pleural fluid, CSF, other forms	Median sensitivity 85% (IQR 75% to 100%); median specificity 100% (IQR 98% to 100%)	Sensitivity 34%; specificity 98%	Sensitivity 96%; specificity 93%
Penz 2015	Up to 15 August 2014	Xpert MTB/RIF	36 (9523)	Lymph node, pleural fluid, CSF, other forms	Sensitivity 69%; specificity 97%	Sensitivity 37%; specificity 98%	Sensitivity 87%; specificity 92%
Sehgal 2016	Up to 31 August 2015	Xpert MTB/RIF	24 (2486)	Pleural fluid	Not applicable	Sensitivity 51%; specificity 99%	Not applicable
Li Y 2017 [c]	Up to 20 June 2015	Xpert MTB/RIF	26 (not reported)	Multiple forms combined	Not reported	Not reported	Not reported
Gupta 2018	Up to 25 March 2017	Xpert MTB/RIF	33 (8977)	CSF	Sensitivity 57%; specificity 98%	Not reported	Not reported
Pormohammad 2019	Upto 11 Nov 2018	Xpert MTB/RIF	16 (not reported)	CSF	Sensitivity 61%; specificity 99%	Not reported	Not reported
Yu 2019	Up to 6 July 2018	Xpert MTB/RIF	21(1629)	Lymph node	Not reported	Not reported	Sensitivity 84%; specificity: 91%
Zhang 2020 [d]	Up to 20 May 2019	Xpert Ultra	7 (1500)	Multiple specimens	Not reported	Not reported	Not reported

Abbreviations: CI: confidence interval; CSF: cerebrospinal fluid: IQR: interquartile range; TB: tuberculosis.

[a]For all forms of extrapulmonary tuberculosis combined, Chang 2012 reported pooled sensitivity and specificity of 80.4% (95% confidence interval (CI) 75.0 to 85.1) and 86.1% (95% CI 83.5 to 88.4), respectively.

[b]Using a composite reference standard, Denkinger 2014 found the following pooled sensitivity and specificity estimates: lymph node tuberculosis (aspirate or tissue) 81.2% (95% CI 72.4 to 87.7) and 99.1% (95% CI 94.5 to 99.9); pleural tuberculosis 21.4% (95% CI 8.8 to 33.9) and 100% (95% CI 99.4 to 100); and meningeal TB 62.8% (95% CI 47.7 to 75.8) and 98.8% (95% CI 95.7 to 100), respectively.

[c]For both pulmonary and extrapulmonary tuberculosis, review authors included 106 studies involving 52,410 specimens. For all forms of extrapulmonary tuberculosis combined, Li Y 2017 reported pooled sensitivity and specificity of 80% (95% CI 69 to 88) and 97% (95% CI 94 to 98), respectively.

[d] Zhang 2020 included 7 studies involving 1500 specimens. For all forms of extrapulmonary tuberculosis combined, pooled sensitivity and specificity were 85.1% (95% CI 76.7 to 90.8%) and 95.7% (95% CI 87.9 to 98.6%), respectively.

Shen 2019 provided pooled estimates for bone or joint tuberculosis. The review included 14 studies with 1884 specimens with a pooled sensitivity of 96% and specificity of 85%.

Table 9. Prespecified changes for review update 2021

Protocol section	Appraisal points	Address here
Background and research question	• Review and update Background section, including supporting references to take account of any changes that may have occurred. This should include updating any new information and current policy debates on the topic	This review update will describe the burden of extrapulmonary tuberculosis worldwide based on the latest WHO Global Tuberculosis Report. The Background will describe the updated WHO guidelines on molecular methods for diagnosing tuberculosis, including Xpert MTB/RIF and Xpert Ultra. The WHO Meeting to update the guidelines took place 3 - 6 December 2019. This Cochrane Review update will have informed these guidelines
Inclusion criteria	• Review current PICO(s) and amend in light of new knowledge. • Identify any changes in usual-care standards. • Check for standardised core outcomes sets, such as those developed in collaboration with the core outcome measures in effectiveness trials (COMET) initiative (www.comet-initiative.org) or by guideline groups since the original review. • Check for any relevant patient-reported outcomes to include subsequent to the original review. • Consider any new studies with less risk of bias that might warrant a stricter study design inclusion criterion (where the older version, when there was a dearth of evidence, included observational or quasi-randomised comparisons).	This is a diagnostic test accuracy review. Participants, index tests, and target condition, will be the same as in Kohli 2018 except as follows: The update will be restricted to adults (15 years and older). The reason for this is that we have a separate Cochrane Review underway that is evaluating the tests for extrapulmonary tuberculosis in children. We will add a composite reference standard, defined as culture or clinical criteria as defined by the primary study authors. The addition of a composite reference standard was specifically requested by the WHO and Guideline members. The primary objectives are to assess the diagnostic accuracy of Xpert Ultra for the diagnosis of extrapulmonary tuberculosis and to assess the diagnostic accuracy of Xpert Ultra for the detection of rifampicin resistance in adults. Secondary objectives are the following. - to investigate potential sources of heterogeneity in test accuracy, including volume of CSF for TB meningitis and processing methods for lymph node TB - to compare the accuracy of Xpert Ultra and Xpert MTB/RIF in studies that evaluated both tests. Concerning patient outcomes, the Discussion will summarize and refer to key findings in the test-treatment Cochrane Review by Haraka et al. (currently undergoing peer review). Although the Haraka review relates to pulmonary tuberculosis, it is the only evidence on patient outcomes of which we are aware.
Methods	-	We will use QUADAS-2 to appraise methodological quality of included studies consistent with Kohli 2018. If data are sufficient, we will perform meta-analyses using a bivariate random-effects model. The analyses will include: 1. Xpert Ultra for different forms of extrapulmonary tuberculosis, culture reference standard 2. Xpert Ultra for different forms of extrapulmonary tuberculosis, composite reference standard 3. Accuracy of Xpert Ultra versus Xpert MTB/RIF in studies that evaluated both tests 4. Xpert Ultra for detecting rifampicin resistance

Table 9. Prespecified changes for review update 2021 *(Continued)*

	The different forms (and corresponding specimens for diagnosis) of extra-pulmonary TB include: tuberculous meningitis, lymph node tuberculosis, pleural tuberculosis, genitourinary tuberculosis, bone or joint tuberculosis. We will create 'Summary of findings' tables for the two primary objectives of the review.

TB: tuberculosis.
This table was approved by the CIDG editorial team on 17 December 2019.

APPENDICES

Appendix 1. Detailed search strategies

MEDLINE (OVID)

1 Mycobacterium tuberculosis/

2 Tuberculosis/ or "Tuberculosis, Multidrug-Resistant"/ or Extensively Drug-Resistant Tuberculosis/

3 (Tuberculosis or MDR-TB or XDR-TB or "Multidrug Resistant Tuberculosis" or "Extensively Drug Resistant Tuberculosis" or tuberculous).ti. ab .

4 (extrapulmonary or extra-pulmonary or EPTB).ti. ab .

5 (lymphadenitis or disseminated or miliary or pleur* or skeletal or spine or mening* or intracranial or intra-ocular or ocular or abdominal or splenic or genitourinary or pericardial).ti. ab .

6 "Tuberculosis, Central Nervous System"/ or "Tuberculosis, Urogenital"/ or "Tuberculosis, Splenic"/ or "Tuberculosis, Spinal"/ or "Tuberculosis, Renal"/ or "Tuberculosis, Pleural"/ or "Tuberculosis, Osteoarticular"/ or "Tuberculosis, Oral"/ or "Tuberculosis, Ocular"/ or "Tuberculosis, Meningeal"/ or "Tuberculosis, Lymph Node"/ or "Tuberculosis, Laryngeal"/ or "Tuberculosis, Hepatic"/ or "Tuberculosis, Gastrointestinal"/ or "Tuberculosis, Female Genital"/ or "Tuberculosis, Endocrine"/ or "Tuberculosis, Cutaneous"/ or "Tuberculosis, Cardiovascular"/ or Tuberculosis, Miliary/ or Tuberculosis, Male Genital/

7 1 or 2 or 3

8 4 or 5

9 7 and 8

10 9 or 6

11 Xpert*.ti. ab .

12 (GeneXpert or cepheid).ti.ab .

13 (near* patient or near-patient).ti.ab

14 11 or 12 or 13

15 10 and 14

Embase (OVID)

1 Tuberculosis, Multidrug-Resistant/ or Extensively Drug-Resistant Tuberculosis/ or Tuberculosis/ or tuberculosis.mp. or Mycobacterium tuberculosis/

2 (MDR-TB or XDR-TB).mp.

3 1 or 2

4 (extrapulmonary or extra-pulmonary or EPTB).ti. or (extrapulmonary or extra-pulmonary or EPTB).ab.

5 (lymphadenitis or disseminated or miliary or pleur* or skeletal or spine or mening* or intracranial or intra-ocular or ocular or abdominal or genitourinary or pericardial).ti. or (lymphadenitis or disseminated or miliary or pleur* or skeletal or spine or mening* or intracranial or intra-ocular or ocular or abdominal or genitourinary or pericardial).ab.

6 tuberculous.ti. or tuberculous.ab.

7 3 or 6

8 Tuberculosis, Central Nervous System/ or Tuberculosis, Hepatic/ or Tuberculosis, Male Genital/ or Tuberculosis, Spinal/ or Tuberculosis, Cutaneous/ or Tuberculosis, Urogenital/ or Tuberculosis, Osteoarticular/ or Tuberculosis, Endocrine/ or Tuberculosis, Renal/ or Tuberculosis, Splenic/ or Tuberculosis, Ocular/ or Tuberculosis, Laryngeal/ or Tuberculosis, Gastrointestinal/ or Tuberculosis/ or Tuberculosis, Meningeal/ or Tuberculosis, Oral/ or Tuberculosis, Pleural/ or Tuberculosis, Lymph Node/ or Tuberculosis, Female Genital/ or Tuberculosis, Miliary/ or Tuberculosis, Cardiovascular/

9 4 or 5 or 8

10 7 and 9

11 xpert*TB.mp.

12 Xpert* MTB RIF.ti. or Xpert* MTB RIF.ab.

13 (GeneXpert or cepheid).ti. or (GeneXpert or cepheid).ab.

14 (near* patient or near-patient).ti. or (near* patient or near-patient).ab.

15 12 or 13 or 14

16 10 and 15

Indexes=SCI-EXPANDED, CPCI-S, Biosis previews

TOPIC

(tuberculosis or tuberculous) *AND* **TOPIC:** (extrapulmonary or extra-pulmonary or EPTB or lymphadenitis or disseminated or miliary or pleur* or skeletal or spine or mening* or intracranial or intra-ocular or ocular or abdominal or genitourinary or pericardial) *AND* **TOPIC:** (Xpert* or Genexpert or cepheid)

LILACS

tuberculosis or tuberculous [Words] and Xpert$ or Genexpert or cepheid [Words]

SCOPUS

(TITLE-ABS-KEY (tuberculosis OR tuberculous) AND TITLE-ABS-KEY (extrapulmonary OR extra-pulmonary OR eptb OR lymphadenitis OR disseminated OR miliary OR pleur* OR skeletal OR spine OR mening* OR intracranial OR intra-ocular OR ocular OR abdominal OR genitourinary OR pericardial) AND TITLE-ABS-KEY (xpert* OR genexpert OR cepheid))

Cochrane Infectious Diseases Group Specialist Register; ClinicalTrials.gov, WHO ICTRP, ISRCTN registry, ProQuest Dissertations & Theses A&I

tuberculosis and Xpert$; tuberculosis and Genexpert; tuberculosis and Cepheid.

Appendix 2. Data extraction form

Data extractor	MK KRS
First study author	
Corresponding study author and email	
Title of paper	
Journal	

(Continued)

Language if other than English
Year

I. Study details

Type of study: randomized controlled trial; cross-sectional cohort (with follow-up); case-control (exclude); unclear/not reported

Study data collection: prospective; retrospective; unclear/not reported

Participant selection: convenience; consecutive; random; other; unclear/not reported

Country:

Country income status: low; middle; high

II. Presenting signs and symptoms, setting

Presenting signs and symptoms?

Clinical setting: inpatient; outpatient; both; unclear/not reported

Level of laboratory running Xpert? peripheral; intermediate; central (reference)

Comments, describe exclusions

(Tests at laboratory levels)

Peripheral: AFB (Ziehl-Neelsen, Auramine-rhodamine, Auramine-O staining) and Xpert MTB/RIF

Intermediate: peripheral laboratory tests and culture on solid media and line probe assay (LPA) from smear-positive sputum

Central: intermediate laboratory tests and culture on liquid media and DST (first- and second-line anti-TB drugs) on solid or in liquid media and LPA on positive cultures and rapid speciation tests

III. Other demographics

HIV patients included? yes; no; unclear/not reported; if yes ## and percentage? (*denominator is number tested, when possible*)

Age? Median age in years (IQR); mean (SD); range; unclear/not reported

Children (< 15 years old) included: yes; no; unclear/not reported; if yes, percentage?

Percentage female included? Unclear/not reported

Past history of TB? yes; no; unclear/not reported; if yes, percentage?

Only patients who received TB treatment for ≤ 7 days were included? yes; no; unclear/not reported; if no, percentage on treatment included?

IV. Reference standard

A. Reference standard for TB detection

Solid culture (specify): LJ 7H10 7H11; other

Liquid culture (specify): MGIT Bactec 460; other

Solid and liquid culture (indicate which kind above)

Were reference standard results interpreted without knowledge of index test results? yes; no; unclear/not reported

B. Composite reference standard for pleural TB

Solid culture (specify): LJ 7H10 7H11; other

Liquid culture (specify): MGIT Bactec 460; other

Solid and liquid culture (indicate which kind above)

Histopathology (specify): granulomas; caseating granulomas

Were reference standard results interpreted without knowledge of index test results? yes; no; unclear/not reported

Did all patients receive the same reference standard? yes; no; unclear/not reported; if no, describe

C. Reference standard for rifampicin resistance

LJ DST MGIT DST MTBDR*plus*

Were reference standard results interpreted without knowledge of index test results? yes; no; unclear/not reported

V. Sites with more than five specimens (check all that apply)

A. Lymph node TB fluid; tissue; both fluid and tissue

B. Pleural TB fluid; tissue; both fluid and tissue

C. TB meningitis CSF

D. Bone or joint TB fluid; tissue; both fluid and tissue

E. Genitourinary TB urine; other, specify

F. Peritoneal TB fluid; tissue; both fluid and tissue

G. Pericardial TB fluid; tissue; both fluid and tissue

H. Disseminated TB blood

I. Other, specify

VI. Specimen processing for Xpert

Condition of specimens: fresh frozen

If frozen for > 7 days, indicate WHO not followed

For a given site, how many specimens were collected per patient? one; multiple; unclear/not reported

A. Lymph node tissue, other tissue

Was the WHO standard operating procedure (SOP) followed for each specimen type?

1a. Lymph node tissue WHO followed: yes; no; unclear

1b. Lymph node tissue homogenization step for tissue specimens: yes; no; unclear/not reported

2a. Other tissue, specify WHO followed: yes; no; unclear

2b. Other tissue homogenization step for tissue specimens: yes; no; unclear/not reported

(For tissue, if WHO SOP not followed, briefly describe specimen processing in comments.)

WHO SOPs for specimen processing; lymph node and other tissue; sterile specimen

1. *Cut the tissue specimen into small pieces in a sterile mortar.*
2. *Add approximately 2 mL of sterile phosphate buffered saline (PBS).*
3. *Grind solution of tissue and PBS until homogeneous suspension has been obtained.*
4. *Place approximately 0.7 mL of the homogenized tissue in a sterile, conical screw-capped tube.*
5. *Double volume of specimen with Xpert® Sample Reagent (1.4 mL Sample Reagent to 0.7 mL of homogenized tissue).*
6. *Shake tube vigorously 10 to 20 times or vortex for at least 10 seconds.*
7. *Incubate specimen for 10 minutes at room temperature, and again shake specimen 10 to 20 times or vortex for at least 10 seconds.*
8. *Incubate specimen at room temperature for an additional 5 minutes.*
9. *Transfer 2mL to Xpert® MTB/RIF cartridge.*

10.*Load into GeneXpert and per manufacturer's instructions.*

(Note: For specimens **not collected in a sterile manner,** WHO SOP suggests an NaOH decontamination/concentration protocol similar to that used for sputum.)

B. CSF

3a. CSF WHO followed: yes; no; unclear

3b. CSF concentration step: yes; no; unclear/not reported

3c. CSF sample input volume: specify; unclear/not reported

(For CSF, if WHO SOP not followed, briefly describe specimen processing in comments.)

WHO SOPs for CSF

If more than 5 mL of CSF is available for testing.

1. *Transfer all of the CSF specimen to a conical centrifuge tube and concentrate the specimen at 3000 × g for 15 minutes.*
2. *Resuspend the pellet to a final volume of 2 mL by adding Xpert® MTB/RIF Sample Reagent.*
3. *Transfer 2 mL of the resuspended CSF sample to the Xpert® MTB/RIF cartridge.*
4. *Load the cartridge into the GeneXpert instrument according to the manufacturer's instructions.*

If 1 mL to 5 mL of CSF is available.

1. *Add an equal volume of Sample Reagent to the CSF.*
2. *Mix the specimen and the Sample Reagent by vortexing as described above. After seven to eight minutes at room temperature, vortex the sample as above a second time.*
3. *Incubate for an additional seven to eight minutes (15 minutes total incubation) at room temperature.*
4. *Add 2 mL of the sample mixture directly to the Xpert® MTB/RIF cartridge.*
5. *Load the cartridge into the GeneXpert instrument according to the manufacturer's instructions.*

C. Body fluids, other than CSF

4a. Body fluid: specify; processed as per manufacturer for sputum

Yes/No/Unclear

4b. Body fluid: specify; sample input volume: specify; unclear/not reported

5a. Body fluid: specify; processed as per manufacturer for sputum (WHO followed)

Yes/No/Unclear

5b. Body fluid: specify; sample input volume: specify; unclear/not reported

(Add additional specimens as needed.)

(For body fluids other than CSF, if manufacturer's instructions not followed, briefly describe specimen processing in comments.)

Manufacturer's instructions for sputum

Raw specimen

1. *Pour or pipette (pipette not provided) approximately 2 times the volume of Sample Reagent into the specimen (2:1 dilution, Sample Reagent: specimen).*
2. *Shake vigorously 10 to 20 times or vortex for at least 10 seconds.*
3. *Incubate sample for a total of 15 minutes at 20°C to 30°C.*
4. *Between 5 and 10 minutes into the incubation period, shake vigorously 10 to 20 times or vortex for at least 10 seconds.*

Specimen sediment

Assay requires at least 0.5 mL of resuspended specimen sediment after digestion, decontamination, and concentration.

1. *Use the method of Kent and Kubica and resuspend the sediment in a 67 mM phosphate/H_2O buffer.*
2. *After resuspension, keep at least 0.5 mL of the resuspended sediment for the Xpert® MTB/RIF assay.*

3. *Add 1.5 mL of Sample Reagent to 0.5 mL of the resuspended sediment (3:1 dilution, Sample Reagent: specimen)*
4. *Follow steps 2 to 4 above.*

Comments on specimen processing.

VII. Specimen processing for culture

Specimen collected from sterile site: Yes/No/Unclear

Specimen processed for culture as per American Thoracic Society Diagnostic Standards? Yes/No/Unclear

(ATS guidelines: specimens collected from normally sterile sites may be placed directly into the culture medium.)

Note: All specimens such as CSF, pleura, lymph node aspirates and tissues, peritoneal fluid, pericardial fluid, bone or joint fluid and tissue, and urine are considered sterile.

VIII. Results

TB detection: number error or invalid or both Xpert® MTB/RIF results over total number of cultures performed. The denominator includes contaminated cultures and results that were inconclusive.

Unclear/not reported.

RIF resistance: number indeterminate Xpert results (over total number of cultures performed).

Unclear/not reported.

Non-tuberculous mycobacteria (NTM): number of cultures with NTM (over total number of cultures performed).

Unclear/not reported.

IX. Tables

(Non-tuberculous mycobacteria (NTM) should be included as not TB)

Tuberculosis detection (example for Xpert Ultra against culture reference standard; provide additional tables Xpert MTB/RIF and for other extrapulmonary specimens; extract trace results for Xpert Ultra)

Xpert Ultra in lymph node aspirate		**Definite TB**		
		Yes	**No**	**Total**
Xpert Ultra result	**Positive**			
	Negative			
	Total			
	Error/invalid			

Rifampicin resistance detection (for all culture-positive, extrapulmonary specimens)

Rifampicin resistance detection		**Rifampicin resistance**		
		Yes	**No**	**Total**
Xpert result	**Positive**			

(Continued)

	Negative
	Total
	Indeterminate

Abbreviation: TB: tuberculosis.

Appendix 3. Rules for QUADAS-2

Domain 1: patient selection

Risk of bias: could the selection of patients have introduced bias?

Signalling question 1: was a consecutive or random sample of patients enrolled?

We scored "yes" if the study enrolled a consecutive or random sample of eligible patients, "no" if the study selected patients by convenience, and "unclear" if the study did not report the manner of patient selection or we could not tell.

Signalling question 2: was a case-control design avoided?

We did not include in the review studies using a case-control design because this study design, especially when used to compare results in severely ill patients versus those in relatively healthy individuals, may lead to overestimation of accuracy in diagnostic studies. We scored "yes" for all studies.

Signalling question 3: did the study avoid inappropriate exclusions?

We scored "yes" if the study included both smear-positive and smear-negative specimens or included only smear-negative specimens. We judged "no" if the study included only smear-positive specimens or excluded specimens based on physical appearance (such as purulence) or a biochemical analysis (e.g. adenosine deaminase (ADA), cytology (cell analysis)). We scored "unclear" if we could not tell.

Applicability: are there concerns that the included patients and setting do not match the review question?

We were interested in how the index tests performed in patients presumed to have extrapulmonary tuberculosis who were evaluated as they would be in routine practice. We scored "low concern" if patients were evaluated at local hospitals or primary care centres. We scored "high concern" if patients were evaluated exclusively as inpatients at tertiary care centres, except for tuberculous meningitis (we judged low concern) where we would expect patients to be evaluated in tertiary care settings. We scored "unclear concern" if the clinical setting was not reported or if information was insufficient to allow a decision. We also scored "unclear concern" if Xpert testing was done at a reference laboratory and the clinical setting was not reported for the following reason. It was difficult to tell if a given reference laboratory provided services mainly to very sick patients (inpatients in tertiary care) or to all patients, including very sick patients and those with less severe disease (primary, secondary, and tertiary care).

Domain 2: index test

Risk of bias: could the conduct or interpretation of the index test have introduced bias?

Signalling question 1: were the index test results interpreted without knowledge of results of the reference standard?

We answered this question "yes" for all studies because Xpert test results are automatically generated and the user is provided with printable test results. Thus, there is no room for subjective interpretation of test results.

Signalling question 2: If a threshold was used, was it pre-specified?

As the threshold is pre-specified in all versions of Xpert, we answered this question "yes" for all studies.

Applicability: are there concerns that the index test, its conduct, or its interpretation differ from the review question?

We note that variations in execution of the test might affect accuracy estimates. We judged "low concern" if the test was performed according to WHO standard operating procedures (WHO 2014), or if the index test was performed as recommended by the manufacturer for sputum. We scored "high concern" if the test was performed in a way that deviated from these recommendations. We scored "unclear concern" if we could not tell. In studies that evaluated several different types of specimens, we used the following rule: if ≥ 75% of the specimen types were processed per WHO standard operating procedure (SOP) or as per the manufacturer's instructions, we judged "low concern"; if < 50% of the specimen types were processed per WHO SOP or as per the manufacturer's instructions, we scored "high concern"; and if at least 50% to 74% of the specimen types were processed per WHO SOP or as per the manufacturer's instructions, or if we could not tell, we scored "unclear concern".

Domain 3: reference standard

Risk of bias: could the reference standard, its conduct, or its interpretation have introduced bias?

We considered this domain separately for the reference standard for detection of extrapulmonary tuberculosis and the reference standard for detection of rifampicin resistance.

Signalling question 1: is the reference standard likely to correctly classify the target condition?

For detection of extrapulmonary tuberculosis, culture is generally considered the best reference standard. However, limitations are associated with culture; bacterial load is usually low in extrapulmonary tuberculosis, leading to a reduction in the sensitivity of culture. Concerning the conduct of the reference standard (preparation of the specimen for culture), N-acetyl-L-cysteine-sodium hydroxide is routinely used to homogenize, decontaminate, and liquefy non-sterile specimens for TB culture (American Thoracic Society 2000). However, CSF, pleural fluid, and lymph node aspirates are usually considered sterile, and standards specify, "specimens collected from normally sterile sites may be placed directly into the culture medium" (American Thoracic Society 2000). Overly processing (sterile) specimens with N-acetyl-L-cysteine-sodium hydroxide may lead to a decrease in viable TB bacteria and consequently false-negative cultures. We scored "yes" if studies did not use N-acetyl-L-cysteine-sodium hydroxide for processing specimens and "unclear" if studies used N-acetyl-L-cysteine-sodium hydroxide. We discussed this further under Discussion and Strengths and weaknesses of the review.

For detection of rifampicin resistance, culture-based drug susceptibility testing (DST, also called conventional phenotypic method) is considered to be the best reference standard. Line probe assays are also WHO-recommended tests for rifampicin resistance. As we extracted data only for studies that used culture-based DST or line probe assays (most often MTBDRplus), we answered this question "yes" for all studies.

Signalling question 2: were the reference standard results interpreted without knowledge of results of the index test?

We scored "yes" if the reference test provided an automated result (e.g. MGIT 960), if blinding was explicitly stated, or if it was clear that the reference standard was performed at a separate laboratory and/or was performed by different people. We scored "no" if the study stated that the reference standard result was interpreted with knowledge of the Xpert Ultra or Xpert MTB/RIF test result. We scored "unclear" if we could not tell.

Signalling question 3: (rifampicin resistance) were the reference standard results interpreted without knowledge of results of the index test?

We added a signalling question for rifampicin resistance detection. We scored "yes" if the reference test provided an automated result (e.g. MGIT 960), if solid culture was performed followed by speciation, if blinding was explicitly stated, or if it was clear that the reference standard was performed at a separate laboratory or was performed by different people, or both. We scored "no" if the study stated that the reference standard result was interpreted with knowledge of the Xpert test result. We scored "unclear" if we could not tell. Not all studies evaluated detection of rifampicin resistance; therefore this question was not applicable to all studies.

Applicability: are there concerns that the target condition as defined by the reference standard does not match the question?

We judged "high concern" if included studies did not speciate mycobacteria isolated in culture, "low concern" if speciation was performed, and "unclear concern" if we could not tell. If a study performed sequencing, we considered the speciation yes. If the study only used a composite reference standard, we considered applicability unclear.

Domain 4: flow and timing

Risk of bias: could the patient flow have introduced bias?

Signalling question 1: was there an appropriate interval between the index test and the reference standard?

In most included studies, we expected that specimens for index test and verification by culture (or a composite reference standard) would be obtained at the same time, when patients were evaluated for presumptive extrapulmonary tuberculosis. However, even if there were a delay of several days between index test and reference standard, tuberculosis is a chronic disease, and we considered misclassification of disease status to be unlikely, as long as treatment was not initiated in the interim. We judged "yes" if the index test and the reference standard were performed at the same time or if the time interval was less than or equal to seven days, "no" if the time interval was greater than seven days, and "unclear" if we could not tell.

Signalling question 2: did all patients receive the same reference standard?

For the diagnosis of any form of extrapulmonary tuberculosis we answered this question "yes" if all participants in the study or a subset of participants in the study (for whom we extracted data) received the acceptable reference standard either culture or a composite reference standard. Regarding culture, we acknowledge that it is possible that some specimens could undergo solid culture and others liquid culture as the reference standard. This could potentially result in variations in accuracy, but we think the variation would be minimal.

For rifampicin resistance detection, we answered "yes" if all participants received the same reference standard (either culture-based DST or MTBDR*plus*), "no" if not all participants received the same reference standard, and "unclear" if we could not tell.

Signalling question 3: were all patients included in the analysis?

We determined the answer to this question by comparing the number of patients enrolled with the number of patients included in the 2 × 2 tables. We answered "yes" if the numbers matched and "no" if there were patients enrolled in the study who were not included in the analysis. We answered "unclear" if we could not tell.

Judgements for overall 'Risk of bias' assessments.

- If we answered all signalling questions for a domain "yes", then we scored risk of bias as "low".
- If we answered all or most signalling questions for a domain "no", then we scored risk of bias as "high".
- If we answered only one signalling question for a domain "no", we discussed further the "risk of bias" judgement.
- If we answered all or most signalling questions for a domain "unclear", then we scored risk of bias as "unclear".
- If we answered only one signalling question for a domain "unclear", we discussed further the "risk of bias" judgement for the doma

Appendix 4. OpenBugs

In this section we provide OpenBUGS models for the bivariate meta-analysis as well as the latent class meta-analysis. Any alternative prior distributions used are provided in the comments within each model.

BIVARIATE MODEL ASSUMING PERFECT CULTURE REFERENCE TEST

```
model {

for(i in 1:N) { # N is the number of studies

############################## LIKELIHOOD
logit(TPR[i]) <- l[i,1]
logit(FPR[i]) <- -l[i,2]
pos[i]<-TP[i]+FN[i]
neg[i]<-TN[i]+FP[i]
TP[i] ~ dbin(TPR[i],pos[i])
FP[i] ~ dbin(FPR[i],neg[i])
se[i] <- TPR[i]
sp[i] <- 1-FPR[i]
l[i,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])
}
############################## HYPER PRIOR DISTRIBUTIONS
mu[1] ~ dnorm(0,0.25) # replaced by mu[1] ~ dnorm(0, 0.01) in sensitivity analysis to check impact of less informative prior
mu[2] ~ dnorm(0,0.25) # replaced by mu[2] ~ dnorm(0, 0.01) in sensitivity analysis to check impact of less informative prior
T[1:2,1:2]<-inverse(TAU[1:2,1:2])
#### BETWEEN-STUDY VARIANCE-COVARIANCE MATRIX
TAU[1,1] <- tau[1]*tau[1]
TAU[2,2] <- tau[2]*tau[2]
TAU[1,2] <- rho*tau[1]*tau[2]
TAU[2,1] <- rho*tau[1]*tau[2]
tau[1]<-pow(prec[1],-0.5) # replaced by tau[1] ~ dunif(0,3) in sensitivity analysis to check impact of less informative prior
tau[2]<-pow(prec[2],-0.5) # replaced by tau[2] ~ dunif(0,3) in sensitivity analysis to check impact of less informative prior
sigma.sq[1] <- pow(tau[1], 2)
sigma.sq[2] <- pow(tau[2], 2)
#### prec = between-study precision in the logit(sensitivity) and logit(specificity)
prec[1] ~ dgamma(2,0.5) # replaced by prec[1] <- 1/pow(tau[1],-2) in sensitivity analysis to check impact of less informative prior
prec[2] ~ dgamma(2,0.5) # replaced by prec[2] <- 1/pow(tau[2],-2) in sensitivity analysis to check impact of less informative prior
rho ~ dunif(-1,1)
############################## OTHER PARAMETERS OF INTEREST
#### POOLED SENSITIVITY AND SPECIFICITY
Pooled_S<-1/(1+exp(-mu[1]))
Pooled_C<-1/(1+exp(-mu[2]))
#### POOLED POSITIVE AND NEGATIVE LIKELIHOOD RATIOS
PLR <- Pooled_S/(1-Pooled_C)
NLR <- (1-Pooled_S)/Pooled_C
#### PREDICTED SENSITIVITY AND SPECIFICITY IN A FUTURE STUDY
l.new[1:2] ~ dmnorm(mu[],T[,])
sens.new <- 1/(1+exp(-l.new[1]))
spec.new <- 1/(1+exp(-l.new[2]))
```

```
} #### END OF PROGRAM
```

LATENT CLASS META-ANALYSIS MODEL

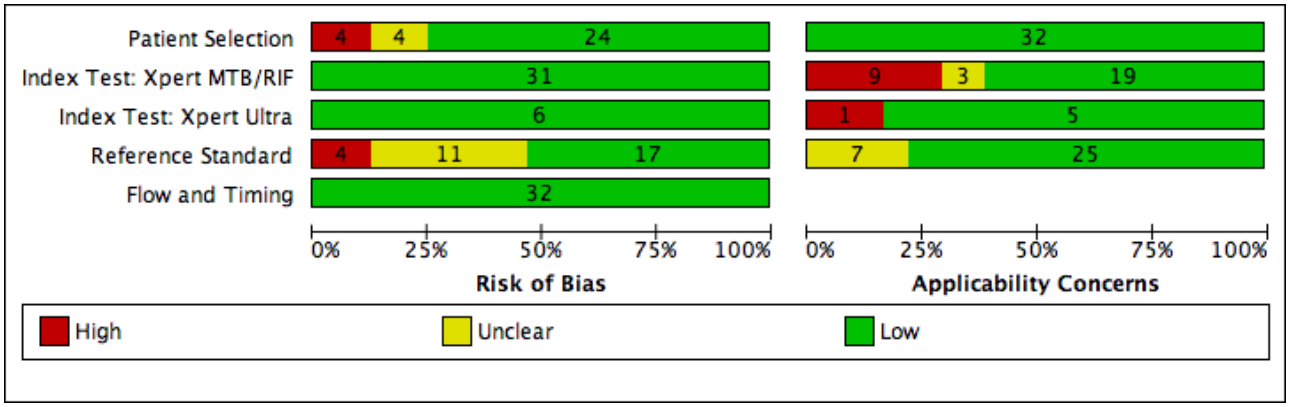
```
# WinBUGS PROGRAM FOR ESTIMATING A BIVARIATE HIERARCHICAL META-ANALYSIS MODEL
# FOR SENSITIVITY AND SPECIFICITY ALLOWING FOR HETEROGENEITY BETWEEN STUDIES
model {
############################## ##############################
for(i in 1:N) {# N is the number of studies
############################## LIKELIHOOD
logit(p[1, i]) <- l[i,1]
logit(p[2, i]) <- -l[i,2]
prob[i,1] <- pi[i]*(p[1,i]* s2[i] + covp[i]) + (1-pi[i])*(p[2,i]*(1-c2[i]) + covn[i])
prob[i,2] <- pi[i]*(p[1,i]* (1-s2[i]) - covp[i]) + (1-pi[i])*(p[2,i]*c2[i] - covn[i])
prob[i,3] <- pi[i]*((1-p[1,i])*s2[i] - covp[i]) + (1-pi[i])*((1-p[2,i])*(1-c2[i]) - covn[i])
prob[i,4] <- pi[i]*((1-p[1,i])*(1-s2[i]) + covp[i]) + (1-pi[i])*((1-p[2,i])*c2[i] + covn[i])
n[i] <- sum(cell[i,1:4])
cell[i,1:4] ~ dmulti(prob[i,1:4],n[i])
pi[i] ~ dbeta(1,1)
se[i] <- p[1,i]
sp[i] <- 1-p[2,i]
l[i,1:2] ~ dmnorm(mu[1:2], T[1:2,1:2])
#==============================================================
# CONDITIONAL DEPENDENCE
#==============================================================
#=======================================
# upper limits of covariance parameters
#=======================================
us[i]<-min(se[i],s2[i])-(se[i]*s2[i]);
uc[i]<-min(sp[i],c2[i])-(sp[i]*c2[i]);
ls[i]<- -(1-se[i])*(1-s2[i])
lc[i]<- -(1-sp[i])*(1-c2[i])
#==============================================================
# prior distribution of transformed covariances on (0,1) range
#==============================================================
covp[i]~dunif(ls[i],us[i]);
covn[i]~dunif(lc[i],uc[i]);
#covn[i]<-0
}
# ==================================
# NON-INFORMATIVE HIERARCHICAL PRIOR DISTRIBUTION OVER REF STD PROPERTIES
# ==================================
for(j in 1:29) {
logit(s2[j]) <- l2[j,1]
logit(c2[j]) <- l2[j,2]
l2[j,1:2] ~ dmnorm(mu2[1:2], T2[1:2,1:2])
}
############################## HYPER PRIOR DISTRIBUTIONS ##############################
#############################################################
#############################################################
###
### XPERT TEST
###
#############################################################
#############################################################
mu[1] ~ dnorm(0,0.25)
mu[2] ~ dnorm(0,0.25) #dnorm(4.59512,10)
T[1:2,1:2]<-inverse(TAU[1:2,1:2])
#### BETWEEN-STUDY VARIANCE-COVARIANCE MATRIX
TAU[1,1] <- tau[1]*tau[1]
TAU[2,2] <- tau[2]*tau[2]
TAU[1,2] <- rho*tau[1]*tau[2]
```

```
TAU[2,1] <- rho*tau[1]*tau[2]
tau[1]<-pow(prec[1],-0.5)
tau[2]<-pow(prec[2],-0.5)
sigma.sq[1] <- pow(tau[1], 2)
sigma.sq[2] <- pow(tau[2], 2)
#### prec = between-study precision in the logit(sensitivity) and logit(specificity)
prec[1] ~ dgamma(2,0.5)
prec[2] ~ dgamma(2,0.5)
rho ~ dunif(-1,1)
############################ OTHER PARAMETERS OF INTEREST
#### POOLED SENSITIVITY AND SPECIFICITY OF XPERT
Pooled_S<-1/(1+exp(-mu[1]))
Pooled_C<-1/(1+exp(-mu[2]))
#### POOLED POSITIVE AND NEGATIVE LIKELIHOOD RATIOS
PLR <- Pooled_S/(1-Pooled_C)
NLR <- (1-Pooled_S)/Pooled_C
#### PREDICTED SENSITIVITY AND SPECIFICITY OF XPERT IN A FUTURE STUDY
l.new[1:2] ~ dmnorm(mu[],T[,])
sens.new <- 1/(1+exp(-l.new[1]))
spec.new <- 1/(1+exp(-l.new[2]))
##########################################################
##########################################################
###
### CULTURE TEST
###
##########################################################
##########################################################
mu2[1] ~ dnorm(0,0.25)
mu2[2] ~ dnorm(0,0.25)
T2[1:2,1:2]<-inverse(TAU2[1:2,1:2])
#### BETWEEN-STUDY VARIANCE-COVARIANCE MATRIX
TAU2[1,1] <- tau2[1]*tau2[1]
TAU2[2,2] <- tau2[2]*tau2[2]
TAU2[1,2] <- rho2*tau2[1]*tau2[2]
TAU2[2,1] <- rho2*tau2[1]*tau2[2]
tau2[1] <-pow(prec2[1],-0.5)
tau2[2] <-pow(prec2[2],-0.5)
sigma.sq2[1] <- pow(tau2[1], 2)
sigma.sq2[2] <- pow(tau2[2], 2)
#### prec = between-study precision in the logit(sensitivity) and logit(specificity)
prec2[1] ~ dgamma(2,0.5)
prec2[2] ~ dgamma(2,0.5)
rho2 ~ dunif(-1,1)
#### POOLED SENSITIVITY AND SPECIFICITY OF CULTURE
S2<-1/(1+exp(-mu2[1]))
C2<-1/(1+exp(-mu2[2]))
s2.new <- 1/(1+exp(-ls2.new))
c2.new <- 1/(1+exp(-lc2.new))
ls2.new ~ dnorm(mu2[1],prec2[1])
lc2.new ~ dnorm(mu2[2],prec2[2])
}
```

Appendix 5. Risk of bias and applicability concerns graph for tuberculous meningitis

Figure 18.

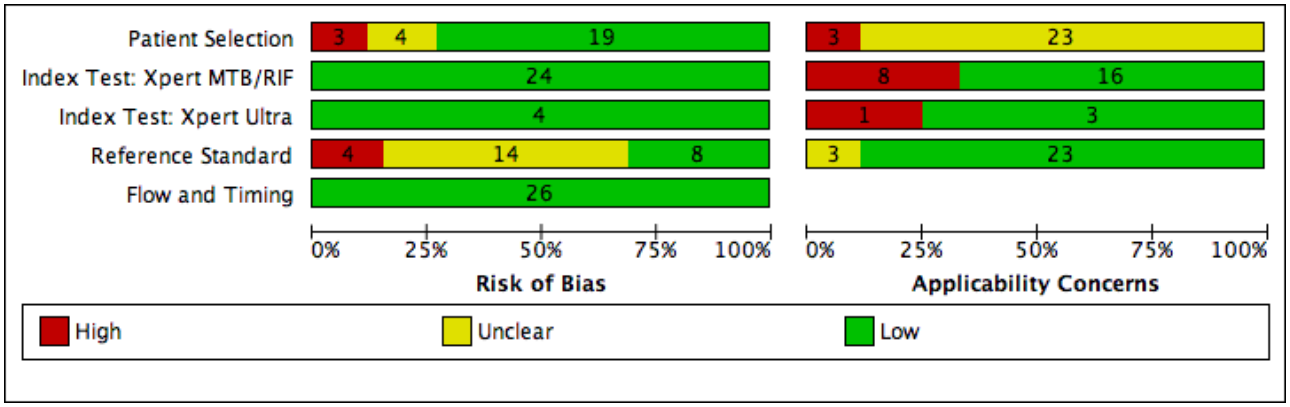
Figure 18. Risk of bias and applicability concerns graph for tuberculous meningitis (cerebrospinal fluid): review authors' judgements about each domain presented as percentages across included studies.



Appendix 6. Risk of bias and applicability concerns graph for pleural tuberculosis

Figure 19.

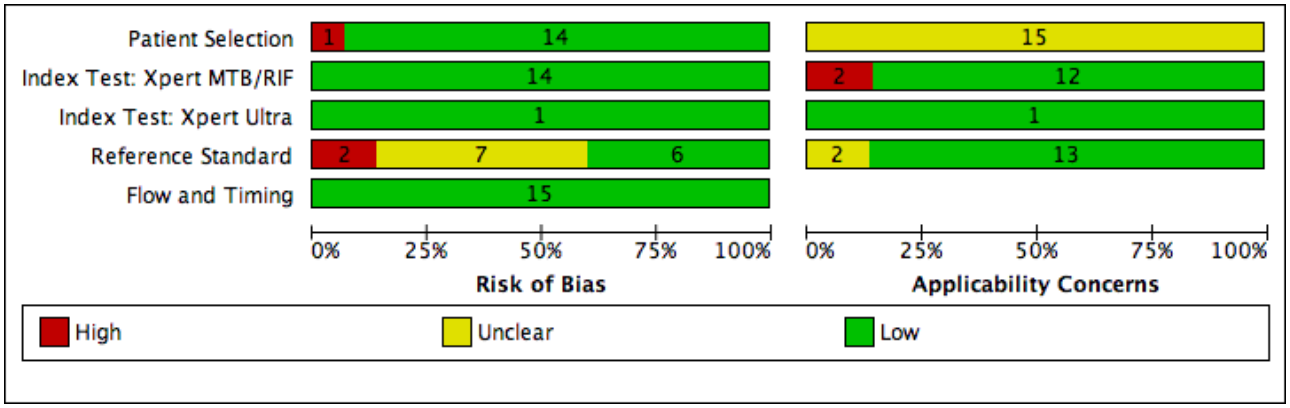
Figure 19. Risk of bias and applicability concerns graph for pleural tuberculosis (pleural fluid): review authors' judgements about each domain presented as percentages across included studies.



Appendix 7. Risk of bias and applicability concerns graph for lymph node tuberculosis

Figure 20.

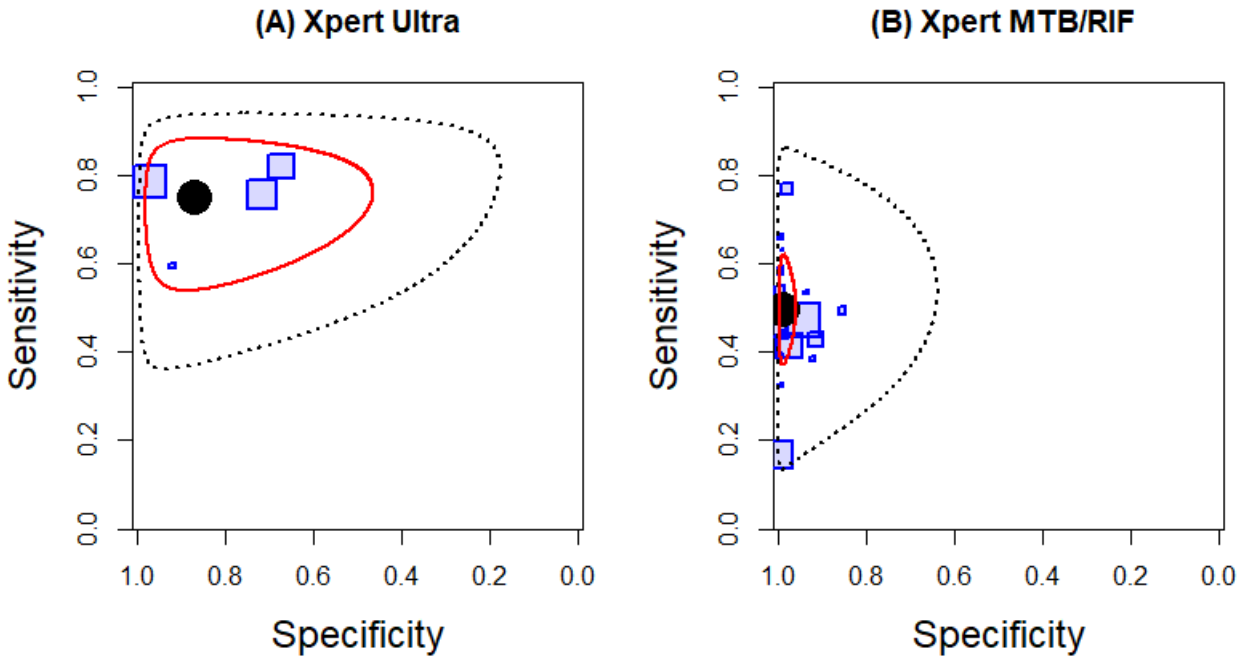
Figure 20. Risk of bias and applicability concerns graph for lymph node tuberculosis (lymph node aspirate): review authors' judgements about each domain presented as percentages across included studies.



Appendix 8. Receiver operating characteristic plot for pleural fluid, Xpert Ultra

Figure 21 displays the receiver operating characteristic (SROC) plots for Xpert Ultra (4 studies) and Xpert MTB/RIF (25 studies) in pleural fluid for pleural tuberculosis.

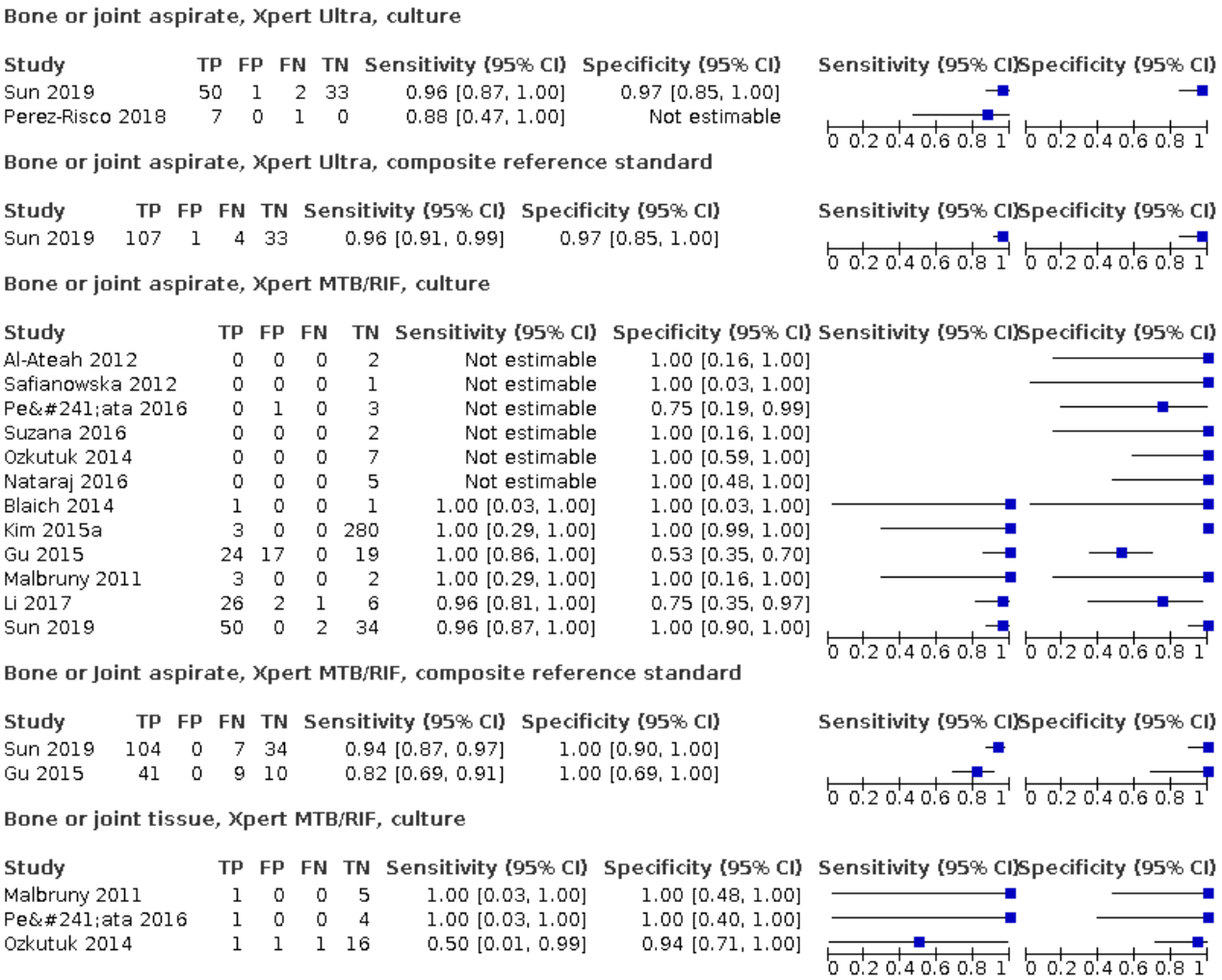
Figure 21. Summary plots of the sensitivity and specificity of Xpert Ultra (A) (4 studies) and Xpert MTB/RIF (B) (25 studies) in pleural fluid for detection of pleural tuberculosis. Each individual study is represented by a shaded square. The size of the square is proportional to the sample size of the study such that larger studies are represented by larger squares. The filled circle is the median pooled estimate for sensitivity and specificity. The solid curves represent the 95% credible region around the summary estimate; the dashed curves represent the 95% prediction region.



Appendix 9. Bone or joint tuberculosis, Xpert Ultra and Xpert MTB/RIF

Figure 22 displays forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in bone or joint aspirate and tissue.

Figure 22. Forest plots of Xpert MTB/RIF and Xpert Ultra sensitivity and specificity in bone or joint fluid and tissue by reference standard. The squares represent the sensitivity and specificity of one study, the black line its confidence interval. FN: false-negative; FP: false-positive; TN: true-negative; TP: true-positive.



Appendix 10. Peritoneal, pericardial, disseminated tuberculosis, Xpert Ultra and Xpert MTB/RIF

Figure 16 displays forest plots of Xpert Ultra and Xpert MTB/RIF sensitivity and specificity in peritoneal fluid and tissue, pericardial fluid, and blood.

WHAT'S NEW

Date	Event	Description
11 January 2021	New citation required but conclusions have not changed	We updated the literature search and included 22 new studies.
11 January 2021	New search has been performed	We have updated the review with more information. There are no major changes to the conclusions.

HISTORY

Protocol first published: Issue 8, 2017
Review first published: Issue 8, 2018

CONTRIBUTIONS OF AUTHORS

MK and KRS wrote early drafts of the protocol.
CMD and SGS contributed methodological advice.
KD contributed clinical expertise.
CMD and SGS tailored QUADAS-2 to the review.
MK and KRS reviewed the studies and extracted accuracy data.
MK and KRS assessed the methodological quality of included studies.
IS, MY, and ND performed the statistical analyses.
All review authors interpreted the findings.
MK, ND, and KRS wrote the first draft of the review.
MK and KRS prepared the 'Summary of findings' tables.
All review authors contributed to the final manuscript.

DECLARATIONS OF INTEREST

We have no financial involvement with any organization or entity that has a financial interest in, or financial conflict with, the subject matter or materials discussed in the review apart from those disclosed.

MK received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

IS received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland.

ND's participation in this project was supported in part by the Canadian Institutes of Health Research.

MY's participation in this project was supported in part by the Canadian Institutes of Health Research.

KD has no interests to declare.

CMD worked for the Foundation for Innovative New Diagnostics (FIND) until April 2019 and has no other interests to declare.

SGS works for FIND. FIND is a not-for-profit foundation whose mission is to find diagnostic solutions to overcome diseases of poverty in low- and middle-income countries. FIND works closely with the private and public sectors and receives funding from donors and some of its industry partners. FIND has an independent Scientific Advisory Committee and organizational firewalls that protect it against any undue influences in its work or in publication of its findings. More information on FIND's policy and guidelines for working with private sector partners can be found at www.finddx.org/ops-gov/.

KRS received funding from USAID, administered by the World Health Organization Global Tuberculosis Programme, Switzerland, and Cochrane infectious Diseases Group, UK. She has received financial support from McGill University, Canada, and the World Health Organization (WHO) Global Tuberculosis Programme, Switzerland for the preparation of systematic reviews and educational materials, consultancy fees from Foundation for Innovative New Diagnostics (FIND), Switzerland (for the preparation of systematic reviews and GRADE tables), honoraria, and travel support to attend WHO guideline meetings.

SOURCES OF SUPPORT

Internal sources

- Liverpool School of Tropical Medicine, UK

External sources

- Foreign, Commonwealth and Development Office (FCDO), UK

  Project number 300342-104
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- Canadian Institutes of Health Research (CIHR) grant PJT-156039: Evaluating diagnostic accuracy of tests and decision rules in the absence of a perfect reference test: application to extrapulmonary tuberculosis, Canada

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Table 9 describes prespecified changes for this review update.

Selection criteria: We included studies where at least 85% of the participants enrolled were adults, aged 15 years or older, with presumptive extrapulmonary tuberculosis or rifampicin-resistant tuberculosis from all settings and countries. Restricting the age group to adults differs from the original review, where we also included children (Kohli 2018). We did this because children are now included in a separate Cochrane Review, *Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children* (Kay 2020). We excluded studies where we could not disaggregate data on adults from those in children and studies where we could not tell the age of the participants enrolled.

QUADAS-2: we modified QUADAS-2 as follows.

Participant selection domain, applicability: For tuberculous meningitis, owing to the severity of the illness, we judged 'low concern' if participants were evaluated as inpatients at tertiary care centres. In the original review, we judged tertiary care to be a setting of high concern.

Reference standard domain: We clarified that CSF, pleural fluid, and lymph node aspirates are usually considered to be sterile, and standards specify that these specimens may be placed directly into the culture medium. Overly processing specimens may lead to false-negative cultures. We scored 'yes' if studies did not use N-acetyl-L-cysteine-sodium hydroxide for processing sterile specimens and 'unclear' if studies used N-acetyl-L-cysteine-sodium hydroxide.

Investigations of heterogeneity: For specimen volume, we restricted this analysis to CSF because it was most clinically meaningful. For other fluid specimen types, the manufacturer's instructions for sputum were usually followed, requiring 2 mL of input fluid for the Xpert cartridge. In terms of the WHO standard operating procedure for lymph node tissue, we did not investigate this further because 80% (8/10) of the included studies followed the WHO recommendations. In performing the review, it became clear that because a homogenization step is part of the WHO standard operating procedure for preparing tissue specimens, there was no need to perform an additional separate analysis to confirm the presence of a homogenization step. We removed condition of specimen (fresh or frozen) from the analysis, because we identified only six studies in the current review that used frozen specimens, and we had already performed an analysis of this possible source of heterogeneity for the Cochrane Review on Xpert for pulmonary tuberculosis (Steingart 2014).

We have tried to eliminate stigmatizing language, for example, by changing 'suspected tuberculosis' to 'presumptive tuberculosis'.

For Xpert Ultra accuracy for lymph node tuberculosis, owing to insufficient data, we were unable to investigate processing methods for lymph node aspirate.

GRADE: We elaborated on the means of applying GRADE to publication bias: We rated publication bias as undetected (not serious) for several reasons: the comprehensiveness of the literature search and extensive outreach to tuberculosis researchers to identify studies; the presence of only studies that produced precise estimates of high accuracy despite small sample size; and our knowledge about studies that were conducted but not published.

Unlike our previous review, in this update we did not extract information on manufacturers' involvement and funding. As both Xpert Ultra and Xpert MTB/RIF are available at a concessional price for researchers in resource-limited settings, and well-established tests, especially Xpert MTB/RIF, industry donation is rarely pursued. We acknowledge that, in addition to funding, there are other reasons for conflicts of interest, but we did not have time to pursue these. We are aware of a new tool being developed for this purpose: TACIT (Tool for Addressing Conflicts of Interest in Trials: tacit.one). We plan to avail ourselves of this new tool in future updates.

Sensitivity analyses: We stated in our protocol that for Xpert Ultra we would perform a sensitivity analysis by limiting studies to those that included only untreated participants. This information was often not reported in the publications and we did not contact primary study authors specifically about this question. We were therefore unable to confirm that studies met this criterion.

For the 'Summary of findings' tables, we prioritised culture as the reference standard (best reference standard for tuberculosis), apart from lymph node aspirate where we provide evidence using a composite reference standard, because, based on findings from the original review (Kohli 2018), we believe a composite reference is preferable for estimating accuracy.

We added post hoc a sensitivity analysis limiting inclusion to studies that used one specimen per participant.

INDEX TERMS

Medical Subject Headings (MeSH)

Antibiotics, Antitubercular [*therapeutic use]; Bacterial Proteins [*genetics]; DNA-Directed RNA Polymerases [*genetics]; Drug Resistance, Bacterial [*genetics]; False Negative Reactions; False Positive Reactions; Mycobacterium tuberculosis [drug effects] [*genetics] [isolation & purification]; *Reagent Kits, Diagnostic; Reference Standards; Rifampin [*therapeutic use]; Sensitivity and

Specificity; Tuberculosis [cerebrospinal fluid] [*diagnosis] [drug therapy]; Tuberculosis, Meningeal [cerebrospinal fluid] [drug therapy]

MeSH check words

Humans